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SYSTEMIC MEDIATORS OF SURGICAL INJURY*

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I. Introduction

In 1865, when, in Glasgow, Lister for the first time applied carbolic acid to the exposed surfaces of a compound fracture, he may not have helped the patient, but he was starting a train of events whose result even he could not foresee.

In that same year the soldiers before Petersburg, under Grant and Lee, faced the final reckoning which led to Appomattox. Compound fracture was the prime indication for amputation in war surgery of that day. Outside the field hospitals the amputated limbs accumulated like cordwood, as many a shocked soldier-boy wrote home to his family. Amputation, leaving a clean open wound free of retained foreign bodies or necrotic muscle, was far to be preferred to the original fracture as a site for the inevitable septic process. Pus was "laudable" only when it could be seen.

Lister, Semmelweiss, Halsted, and those who followed, on to Florey and Fleming, so controlled surgical sepsis that a systemic response to injury aside from infection was discernible, even though infection when present greatly magnified the underlying response.

Although the centennial of that carbolic-treated compound fracture is drawing near, and although military surgery no longer piles up amputated limbs in quite such profusion, the knowledge of trauma as a distinct area of human biochemistry and metabolism is still in its infancy. Texts of biochemistry and metabolism make but sparse mention of trauma in their long discussion of other endocrine and metabolic changes. It is much easier to find a connected account of the endocrinology and metabolism of hypo- or hyper-adrenocorticism, rare though they are, than it is to find a connected account of the endocrinology and metabolism of such a commonplace thing as a compound fracture. This is true despite the many and important changes in the metabolism of water, fat, carbohydrate, protein, and electrolyte that occur following injury. Only recently in the surgical journals or texts does one begin to find systematic description of these changes, an understanding of which is basic to good surgery.

This communication has as its purpose a brief review of the present status of our knowledge of the systemic mediators, both endocrine and nonendocrine, which alter biochemistry and metabolism after surgery or injury. These are the chemical harbingers that bring, to the bodily tissues remote from the wound, the message of injury. There is comparatively little of direct therapeutic application in this review. I have often likened this area of human knowledge to that concerning the energy cycle in carbohydrate metabolism. Developments in both fields have given the practitioner a basic understanding of the needs of his patients, the action of hormones and drugs, the patient's response, and the dynamics of disease and recovery. Against this background, treatment has changed largely in its more effective application.

II. The Need to Postulate Mediators in Injury; Types of Mediators

When we look at a compound fracture it is apparent enough that mechanical forces disrupted and changed the tissue. When we look at the changing body composition remote from the injury, the changing nature of blood chemistry or urine secretion, the proximate cause of the alteration is not so clear. What forces, reflexes, mediators, or emissaries transmit the message of tissue injury to the uninjured tissues of the body? After extensive operation or severe unanæsthetized injury, changes which we may call "post-traumatic metabolism" are discernible in the bodily economy. These are the result of the sum of the components of the injury, including hæmorrhage, tissue destruction, shock, infection, and starvation.

These diffuse bodily changes of post-traumatic metabolism fall into six broad categories:

1. *Loss of lean body tissues.*—This manifestation is represented by the familiar negative nitrogen balance and by changes in intermediary protein metabolism that involve breakdown in some areas (muscle, for example) and build up in others (for example, albumin, antibodies, the wound). In

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severe injury the degree of nitrogen loss is far greater than that seen in starvation alone, and this loss can be modified only by giving forced intakes of excessive amounts of nourishment. This phenomenon is later followed by a reversal, or anabolic phase, in which body tissues are readily rebuilt even with small intakes.

2. *Loss of intracellular electrolyte and water.*—This accompanies the loss of lean tissue nitrogen, but is larger in quantity than one would predict from the nitrogen loss alone.

3. *Increased renal tubular resorption of extracellular substances (water, sodium chloride, bicarbonate) from the glomerular filtrate.*—This leads to the conservation of water and extracellular salt and positive balances if excess is given.

4. *Mobilization of carbohydrate from the liver.*—This is followed by slight hyperglycæmia and decreased carbohydrate tolerance.

5. *Oxidation of body fat.*—This causes a loss of weight greater than the sum of losses of lean tissue and water, and provides abundant energy from endogenous stores.

6. *Diversion of protein substrates from the lean body mass to the wound.*—The wound undergoes the anabolic changes of growth and protein synthesis, while the lean body mass as a whole is undergoing a net catabolic change.

These diffuse alterations occur after injury and most of them occur in tissues that have not been injured. We must, therefore, seek out the mediators that bring to these tissues the message of injury.

In general there are two types of mediators. First, there are those which do not depend on the endocrine glands to initiate a diffuse change in bodily economy. Second, there are those which appear to depend on known hormones from endocrine glands.

We can further characterize these two types of mediators. The *nonendocrine mediators* are largely harmful. They demand treatment, which is the basis of wound surgery. By contrast, the *endocrine mediators* are often helpful and in most instances (with a few important exceptions) they do not require treatment. Indeed the significance of the endocrine mediators is best appreciated by the total collapse that occurs in their absence.

The *endocrine* mediators are essential to survival, while the *nonendocrine* mediators provide the basic rationale for treatment. Let us first discuss the nonendocrine mediators.

III. The Nonendocrine Stimuli to Bodily Change After Severe Injury

The nonendocrine phenomena that alter body metabolism diffusely after injury may be grouped under six headings (Figs. 1 to 6):

1. *Direct injury to the central nervous system,* with failure to ventilate (anoxia, acidosis), failure to cerebrate, and failure of vasoconstrictor mechanisms.

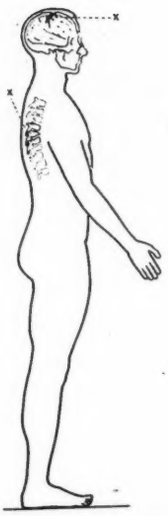

Fig. 1.—Sublethal Injury to the Central Nervous System

a. Inadequate Ventilation
Anoxia
Acidosis

b. Inadequate Vasoconstriction
"Spinal Shock"

c. Inadequate Reflexes and Mentation
Aspiration Pneumonitis
Bronchopneumonia
Coma and Restlessness

Fig. 1.—In this and the following five figures are diagrammed the broad categories of injury which are followed by systemic alterations arising through biochemical mediators other than the endocrine glands. These biochemical changes are responsible for diffuse disorders in tissues remote from the injury.

Sublethal injury to the central nervous system affects body tissues generally through inadequate ventilation, with anoxia and acidosis, inadequate vasoconstriction, and the suppression of normal reflexes (often resulting in aspiration pneumonitis) and mentation.

2. *Injury to the airway,* with failure to ventilate, resulting also in anoxia and acidosis.

3. *Loss of effective blood volume,* due either to hæmorrhage (internal or external) or sequestration of fluid or blood, leading to hypovolæmic and hypotensive shock. This produces anoxia and acidosis, and the prolonged deficiency of flow leads to deficient organ function (liver, brain, kidney) and accumulation of abnormal metabolites.

4. *Cross-sectional destruction of tissue,* with accumulation of extracellular fluid and plasma in the traumatized area, and release into the circulation of intracellular solutes, such as potassium, enzymes, and pigments.

5. *Loss of the normal barriers to infection.*—The skin and the mucous membranes line the body's exterior and interior, and protect it from the swarming bacteria of the outside world and the gastro-intestinal tract. When these barriers are disrupted, contamination occurs, and in due course this contamination becomes infection.

6. *Starvation.*—All wounds of any magnitude are accompanied by starvation of at least transient nature. Starvation makes a contribution to the early losses of body tisues; such contribution is unimportant when compared with the inroads made by early catabolic processes. Later on it becomes an important matter. Starvation of the injured patient (or the postoperative surgical patient) after the first four to seven days becomes most significant in terms of retarded convalescence. At this later stage it is a factor second only to infection as a cause of convalescent failure.

There is not space here to discuss the many surgical manœuvres by which these six sources of abnormal biochemistry are treated surgically to prevent the deterioration that results from their

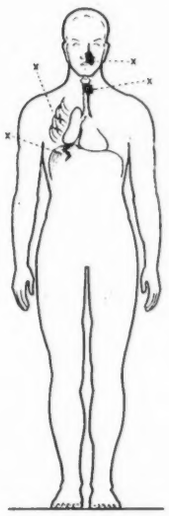

Fig. 2.—Wounds of the Airway

Inadequate Ventilation
1. Anoxia
Cell Death
Cerebral Damage
Renal Insufficiency
2. Respiratory Acidosis
"Too Fast To Compensate"
Hyperkaliemia
Ventricular Fibrillation

Fig. 2.—Wounds of the airway, which may occur at any level of the airway mechanism, affect the metabolism of tissue cells generally through the production of anoxia and respiratory acidosis.

unimpeded progress. The successive steps of surgical care, starting with the simplest first-aid measures and following through major surgery to the last weeks of final convalescence, have as their objective the prevention or treatment of these six sources of disordered body metabolism, which arise directly from the wound itself. Effective wound surgery may be defined as an orderly approach to these six results of the wound. These are six mechanisms which, by a variety of biochemical modalities (acidosis, anoxia, toxicity and energy-lack), transmit the message of injury to the tissues.

IV. The Endocrine Mediators

The endocrine mediators that transmit the message of injury to the body tissues may be listed under four headings.

1. The hypothalamic-pituitary-corticosteroid system.
2. The aldosterone-renal tubular system.
3. The antidiuretic substances-renal tubular system.
4. The operation of catechol amines of the adrenal medulla (epinephrine and norepinephrine) on carbohydrate metabolism and blood flow.

To these one might be tempted to add changes in the gonads, the thyroid, and rate of secretion of growth hormone. Evidence on systematic changes in these endocrine systems is as yet too sketchy to justify their inclusion with the four central endocrine alterations of trauma.

V. Do These Mediators Cause Changes in Body Metabolism After Injury?

What is the evidence that any of these mediators alters body metabolism after injury?

We will not beg the question as regards the nonendocrine stimuli. They are in themselves diffuse metabolic changes, which subside only upon treatment of the wound. When a patient with a wound of the airway becomes anoxic and acidotic, this diffuse biochemical change will not only alter cellular function, but also kill body cells. Oxidative energy exchange is the basis of life, and without it cells die. Oxidative energy exchange will occur only in a restricted range of environmental pH and electrolyte structure. Whether the patient dies of cerebral anoxia, ventricular fibrillation, renal failure, or shock, it is clear that these two nonendocrine mediators—anoxia and acidosis—are the cause of diffuse bodily changes. Using this as an example, we will not further elaborate the fact that the biochemical changes initiated by the wound itself produce diffuse changes in tissue metabolism, largely harmful, leading to deterioration, often fatal and requiring treatment.

But we must look much more closely at the endocrine changes. Are they indeed the cause of diffuse metabolic alterations in the body?

First let us consider the catechol amines of the adrenal medulla, and the adrenergic amines, epinephrine and norepinephrine. There seems to be little doubt that after injury the production of both these substances is increased. The evidence currently available suggests that the most potent stimuli to these substances are fright, apprehension, and other psychic stimuli on the one hand, and hypovolæmic shock on the other. Studies on the adrenal vein blood of the dog demonstrate huge increases in output of catechol amines with blood loss. That these amines produce diffuse vasoconstriction and mobilization of liver glycogen is seldom held open to doubt. Final proof of a rise in peripheral blood levels and resultant physiologic activity should be sought in injured man.

Next we consider the antidiuresis. It has been known for many years that the most trivial form of trauma or even emotional excitement produces a persistent negative free water clearance with marked water retention. The excretion of solute becomes a linear function of water excretion, positive free water clearance (i.e., excretion of a very dilute urine) is never exhibited, and the renal dynamics are characteristic of antidiuretic hormone activity. This antidiuresis occurs quite independent of any alteration in effective renal plasma flow or glomerular filtration rate. Although these very antidiuretic changes, occurring in test animals, have been used as bioassay for antidiuretic hormone, we must reserve judgment on endocrine mechanisms. Chemical identification in post-traumatic man of increased vasopressin secretion or excretion is as yet lacking. We are here viewing the metabolic change itself as possible evidence of the underlying endocrine activation.

The matter of aldosterone activity has come much more recently to the fore. It has been known for several years that in the post-traumatic patient sodium excretion diminishes, that this results in a lowered sodium-potassium ratio in the urine, and that it occurs by increased distal tubular resorption of sodium. The fact that all of these

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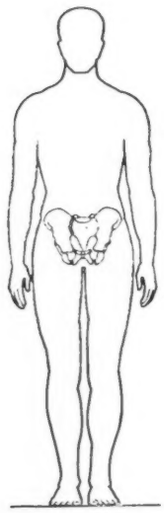

Fig. 3.—Cross-sectional Tissue Injury (Fracture, Muscle Crush, Burn, Laceration)

a. Pain
b. Discontinuity of Structure
c. Necrosis and Anaerobiosis
d. Loss of Skin and Mucosal Barriers
Contamination → Infection
e. Metabolic Acidosis and Ion Exchange
f. Accumulation of Muscle Pigment and Enzymes

Fig. 3.—Cross-sectional tissue injury, as exemplified by fracture (diagrammed here as a fractured pelvis), muscle crush, burn or laceration, affects tissue cells generally through the changes which arise from altered function due to discontinuity of structure itself and necrosis of tissue. In addition, the loss of normal barriers permit contamination and infection. Wounds of this type produce metabolic acidosis through muscle necrosis as well as deficient circulation, and permit the accumulation of muscle pigment and enzymes which are damaging to tissues remote from the injury, most particularly the kidney.

changes are characteristic of aldosterone production and that increased aldosterone production after trauma has now been demonstrated by several workers suggests an association. As is the case with antidiuresis, the changes that occur in the kidney after surgery are so characteristic of aldosterone production that similar changes in experimental animals have been used as a basis for bioassay. Nonetheless, we must again emphasize that definitive experiment and observations have yet to be made, to demonstrate the extent to which the peculiarities of post-traumatic renal handling of water and electrolytes are produced by aldosterone or by other factors including transient changes in renal hæmodynamics.

Turning to the hydroxycorticosteroids, we find here the nub upon which the controversy about metabolic activation finally has turned. What is the evidence concerning the relation of the local wound to the systemic corticoid changes and of these in turn to body chemistry, metabolism, and convalescence? Let us list the facts that seem well established and see what sort of synthesis we can make.

1. After injury there is increased production of ACTH and of corticosteroid in the adrenal vein and in the peripheral blood. This has been shown both in animals and man.

2. Exogenous dosage of adrenal hormones causes a change in metabolism which in certain respects resembles the post-traumatic state and in other respects is very different indeed. The similarities lie largely in the increased tendency to excrete nitrogen and potassium, to decrease the oxidation of carbohydrate in the periphery, and to enlarge the extracellular fluid at the expense of the intracellular fluid. The differences lie in the time-course of activation and in the chronic effects of the two.

3. Patients who have no adrenal glands and are given no replacement do not tolerate trauma. The failure manifests itself by hypotensive hypovolæmic shock. It is vascular, not metabolic, failure, if one can draw a distinction. A shock state (rather than some alteration in nitrogen metabolism) is the fatal result of a lack of corticosteroid hormones after injury. In the untreated experimental situation (and in the unintentional clinical experience) survival is too brief to make observations on nitrogen metabolism, unless steroid replacement is provided.

4. In the adrenalectomized dog or man the amount of hormone required for survival is sharply increased after trauma, as compared with the normal resting situation. Here again the critical parameter seems to be vascular homœostasis.

5. In the adrenalectomized dog or man given constant exogenous dose of hormone the normal post-traumatic sequence—nitrogen loss and potassium loss followed later by anabolism—occurs. The sodium curve, however, is different from that in the intact organism.

6. Closer study of the data mentioned above in (5) demonstrates that the level of hormone in the blood does not in point of fact remain constant after injury, despite the constant dose of hormone in the adrenalectomized state. There is an altered intermediary metabolism of steroid hormones induced by trauma which, working by several mechanisms, both renal and hepatic, results after trauma in a raised concentration of the free (active) steroid in the blood of the adrenalectomized subject even though the exogenous dose of steroid remains constant. From this we can conclude merely that metabolic studies after adrenalectomy on a constant dose of hormone do not cast much light on whether or not altered nitrogen metab-

Fig. 4.—Wound Shock (Oligæmia, Vasoconstriction, Prolonged Deficiency of Flow)

a. Anoxia and Acidosis
Decreased Responsiveness of Vessels "Clinical Taking Up"
b. Sepsis—Anaerobic
c. Visceral Damage
Brain—Liver—Kidney
d. Accumulation of Metabolites

Fig. 4.—In shock there is oligæmia, diffuse vasoconstriction and prolonged deficiency of flow with a resulting diffuse change in cellular metabolism, quite distinct from that seen where shock is absent. Sepsis, particularly anærobic, thrives in the tissues and deficient circulation of a patient in shock. There is anoxic damage to the cells of the parenchymatous viscera. With decreased renal excretion and hepatic function, there is an accumulation of abnormal metabolites, some of which are harmful to the organism.

olism is initiated by a change in blood steroid level.

7. It has been known for many years that alterations in nitrogen metabolism occur after trauma without measurable changes in steroid hormone. Prominent among these is post-traumatic anabolism, which occurs without any significant change in excretion of measured steroid hormones. The period of nitrogen negativity seems somehow to be related more to the nature of the wound and the duration required for healing to "tensile integrity" than to the total hormone secretion. In certain injuries such as fractures and burns one sees persistent nitrogen negativity even with high oral intakes in spite of the fact that the steroid hormone levels are quite normal or even low.

Let us, therefore, summarize this situation as shown in Fig. 7. We see here the familiar activation-chain from the wound to the endocrine change and thence over to metabolism. In addition, post-traumatic metabolism alters the intermediary disposal of the steroid hormones themselves. Notice that there is an arrow directly from the wound to metabolism; there are many evidences that changes in nitrogen metabolism in unwounded tissue are determined at least in part by the stage to which wound healing has progressed. Later occurrences are quite independent of corticosteroid changes.

In summary, we may postulate that the corticosteroids are important in initiating lean tissue catabolism after injury, but other factors are also important and in some cases may predominate. Some of these "other factors" seem to relate to the wound itself, its nature and the question of whether or not it is healed or, if unhealed, infected. It is in the study of nitrogen metabolism and lean tissue change in relation to wound healing that one finds the most suggestive evidence for the existence of some hormone or circulating chemical influence arising from the wound itself.

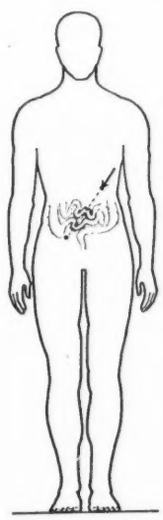

Fig. 5.—Contamination → Infection

a. Loss of Skin and Mucosal Barriers
b. Devitalized Tissue—Foreign Bodies —Mucosal Leak—Closed Space Pressure
c. Special Effects
   Gram Negative Bacilli
   Anaerobes
   Antibiotic Resistance
d. Hypertension—Tachycardia—Fever —Delirium—Oliguria—Azotæmia— Shock—Acidosis—Metastatic Sepsis

Fig. 5.—Contamination leading in turn to infection may arise from any wound. This occurs through the loss of normal anatomical barrier between the sterile internal environment and the bacterial flora surrounding it both within (hollow viscera) and without. Shock may result from infection alone when it is due to Gram-negative bacilli or anaerobes.

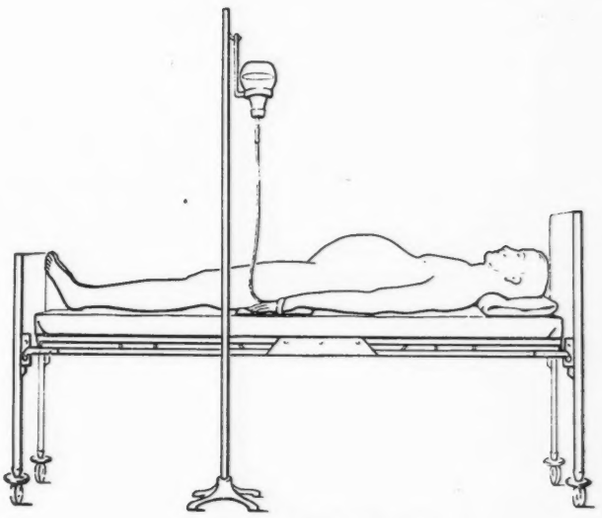

Fig. 6.—Starvation

a. Shift in Energy Source Diet → Endogenous Foodstuffs
b. Glycogenolysis—Gluconeogenesis
c. Lean Tissue Wasting
d. Conservation of Extracellular Fluid
e. Oxidation of Fat
f. Endogenous Water Production

Fig. 6.—Starvation of some degree is an inevitable accompaniment of severe injury. In its early stages it does not appear to be harmful, and large amounts of forced feeding have little clinical effect. As time passes, the starvation factor increasingly alters body composition and cellular activity through the mobilization of energy from fat and glycogen, the wasting of lean tissues with excretion of their nitrogen fraction and the production of endogenous water by fat oxidation, much of which is retained during a period of post-traumatic antidiuresis.

VI. The Negative Nitrogen Balance and Starvation

Early post-traumatic nitrogen loss does comparatively little harm to wound healing itself. The wound heals quite normally in the presence of negative nitrogen balance. On a busy surgical service the wounds of a large fraction of the patients heal to tensile integrity (so that the sutures are removed and gastro-intestinal anastomoses become functional) before nitrogen positivity is attained. This is most especially true in very sick patients, in patients with extensive operations, or in patients with continuing postoperative complications. The wound seems to have a high priority on bodily substances and can achieve its anabolism although the rest of the lean tissues may be engaged in a net catabolic process, even a septic one.

This net catabolic process may not exist throughout all lean tissues simultaneously. Although most tissues may be undergoing wastage, there may be special tissues—of which the wound is one—undergoing an anabolic process at this time. Synthesis of protein, such as hepatic albumin, may be increased after trauma even though muscle cells are wasting away.

The nitrogen lost in postoperative catabolism comes largely from skeletal muscle; it is the only tissue capable of yielding up the very large amounts involved. After bilateral compound fracture of the femur, for instance, an amount of nitrogen representing between four and seven kilograms of lean wet tissue is lost. There is measurable shrinkage of

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lean muscular tissues and these seem to be the nitrogen donor. Skeletal muscle, being the victim of post-traumatic protein catabolism, is also the beneficiary of post-traumatic anabolic gain. It is muscle tissue that increases during the nitrogen anabolism of recovery.

Starvation plays a definite role in the loss of body tissues after injury, but the dynamics of this loss are quite different from those of starvation. It has been known for a long time that lesser degrees of trauma induce only minor or negligible losses of body nitrogen and that these are readily prevented by suitable feeding. As one progresses up the scale to more severe injury, such as multivisceral operations, fractures, and burns, we find that larger and larger amounts of nitrogen and calories are required to maintain any sort of zero balance in the post-traumatic patient. When such heroic regimens are instituted the patient does indeed lose less weight. But it is difficult to discern any other clinical effect that might in any sense be called beneficial.

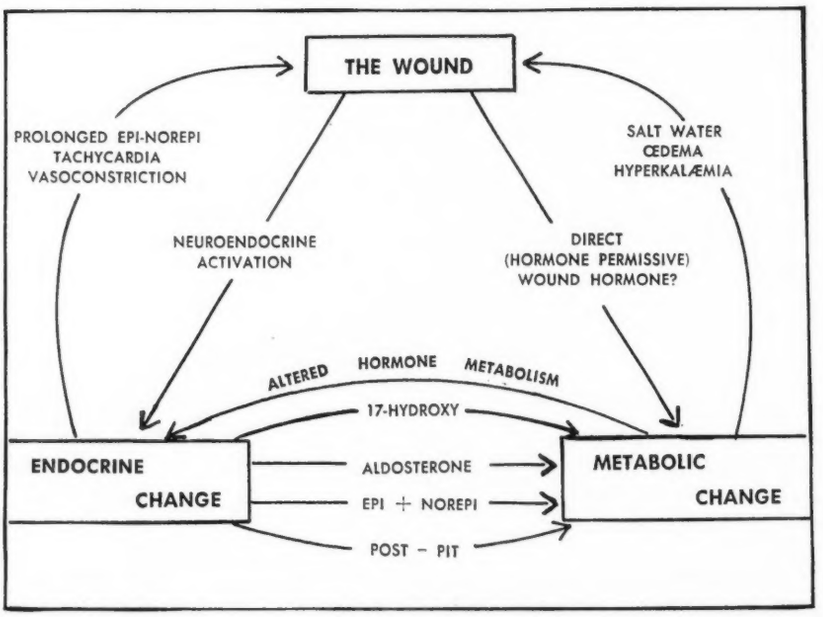

Fig. 7.—Diagrammatic representation of some of the interrelationships between the wound, endocrine change and metabolic alteration. The four endocrine mediators discussed in the text are shown below, as modifying metabolic activity. In addition two pathways are shown by which the wound alters bodily economy. One is a pathway affecting the endocrine glands via the central nervous system and the pituitary. The other is a direct effect of the wound on metabolism, by the nonendocrine stimuli discussed in the text. In addition, the wound affects local tissues directly in a way which alters their cellular activity and initiates the local histochemical sequences of wound-healing. Changes in tissues remote from the wound contribute materials needed locally for healing.

The occasionally damaging effects of endocrine and metabolic activity are shown—excessive adrenomedullary activity or salt-and-water retention—as adding to the burdens imposed by the wound.

Finally, diagrammed below is the altered hormone metabolism which, after injury, results in an abnormal disposal of hormones and thereby constitutes a modality by which post-traumatic metabolism itself alters endocrine activity. This figure is reproduced from the Harvey Lectures.

For example, a normal healthy young man who is "semi-starving" will maintain zero balance on amounts of nitrogen in the general range of 7.0 grams per day with 1500 calories. This same person after a subtotal gastrectomy suddenly increases his requirement for balance to approximately 20 g. of nitrogen a day and 2500 calories. The trauma has so altered the "set" of his tissues that he now requires approximately twice the nourishment he previously did, in order to maintain his lean body mass at a constant weight. Comparatively few definitive experiments have been done on patients after burns, but the evidence suggests that from 40 to 60 g. of nitrogen and from 4000 to 6000 calories would be required to maintain the patient in zero balance right from the start. The trauma-induced change in nitrogen metabolism therefore may be described as "increasing the urinary loss when there is no intake, and increasing the intake required to avoid loss".

It is not true to state that nitrogen loss after severe injury is due "only to starvation", nor is it proper to say that postoperative feeding has nothing to offer the patient's lean tissue mass. The post-traumatic metabolic change is quite different from starvation, and it imposes a much greater need. It is essential to meet this need at least in part, and as soon as practical, by early postoperative feeding when gastro-intestinal acceptance becomes evident.

This early post-traumatic catabolic nitrogen loss which we have been discussing above is quite different from late post-traumatic starvation. The patient with a malfunctioning gastrectomy stoma who is not taking any nourishment after his fifth to seventh day is far different from the person he was in the early days of his postoperative period. He is now truly starving, and the process which is going on in his body has all the earmarks of starvation. Nitrogen loss is low and the tissues are "avid" for nourishment; they readily synthesize protein. Nitrogen loss is completely and easily preventable by feeding if the patient can eat. We therefore differentiate sharply between early post-traumatic catabolic tissue loss and late post-traumatic starvation. This is an example of the dynamic nature of surgical convalescence and the changing day-to-day requirements of the patient.

What causes negative nitrogen balance? The answer is a platitude: a mixture of injury, starvation, infection, and a host of other stimuli. The question is really: what is the mediator? We have already discussed this point and we will not repeat it here save to mention that it is only during the first few days after severe injury that one can make a correlation between total corticosteroid excretion and total nitrogen excretion. After this time there is no correlation, and later anabolism has no characteristic steroid activation.

VII. SUMMARY

Recent endocrinologic research has brought to light a series of four hormonal mediators which bring to the organs and tissues the message of bodily injury. The metabolic meaning of these messages seems clear enough in terms of the catechol amines, aldosterone, and antidiuresis factors, even though quantitative data are sorely needed. As regards the corticosteroids, whose changes in blood and urine are such a characteristic earmark of trauma, evidence is much more varied and the final work has yet to be done. The corticosteroids are necessary for vascular homœostasis. Their lack leads to a shock-like state. Their role in initiating changes in the lean tissue mass as indicated by altered nitrogen metabolism is still uncertain although this alteration was one of the first identifiable sequelæ of trauma.

Increasingly these endocrine alterations are looked upon as normal—to be considered, allowed for, and understood. They are not an indication for treatment unless they are absent. Their absence is most commonly due to prolonged cortisone treatment for other diseases.

Interest in the endocrinology of trauma, no matter how great, should not overshadow the surgeon's concern with the nonendocrine stimuli known since Lister. They are the basis not only of sound wound surgery but also of the systemic deterioration from which normal endocrine defences cannot protect the patient. These are: brain injury, ventilatory deficiency, tissue necrosis, shock, infection, and starvation. These diffuse biochemical harbingers of change and deterioration arise from the wound itself. They change metabolism diffusely and are, in themselves, potent stimuli to endocrine activity. We reduce or remove them when we treat the injured patient surgically. Only when they subside do the endocrine defences of the patient return once again to their resting state so that the patient can pass on into anabolism, later convalescence, and social rehabilitation.

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RÉSUMÉ

Les recherches endocrinologiques récentes ont mis à jour une série de quatre médiateurs hormonaux qui avertissent les organes et les tissus de la présence d'une blessure. La signification métabolique de ces messages semble assez nette pour les catécholamines, l'aldostérone et les facteurs antidiurétiques bien que nous soyons encore courts de précisions quantitatives. En ce qui concerne les corticostéroïdes dont les variations du taux dans l'urine correspondent si bien à toute agression, leurs messages semblent parfois contradictoires et nous avons encore beaucoup de chemin à parcourir avant d'en saisir clairement le sens. Les corticostéroïdes sont nécessaires à l'homœostasie vasculaire. Leur déficience amène un état ressemblant au choc. La part qu'ils prennent dans le déclenchement des altérations portées à la masse des tissus maigres, et reflétées par la perturbation de l'équilibre azoté, est encore mal définie, bien que ces altérations s'inscrivent parmi les effets les plus précoces des traumatismes.

On s'habitue à considérer ces changements endocriniens comme normaux—facteurs à observer, à prendre en considération et à comprendre. Ils ne forment pas d'indication à une thérapie à moins d'être absents. La plupart du temps cette absence est le résultat d'un traitement à la cortisone pour quelqu'autre maladie.

L'intérêt porté à l'aspect endocrinologique de l'agression si grand soit-il ne doit pas remplacer le respect que le chirurgien doit aux facteurs non-endocriniens connus depuis Lister, car non seulement forment-ils la base sur laquelle repose une saine chirurgie des blessures, mais encore sont-ils à la source de la déchéance systémique du malade, contre laquelle les mécanisme endocriniens normaux de défense n'offrent aucune protection. Au nombre des ces dangers nous comptons les blessures au cerveau, les déficiences ventilatoires, la nécrose des tissus, l'infection et la carence nutritive. Ces avant-coureurs biochimiques annoncant les perturbations et la déchéance partent de la plaie même et parcourent l'organisme entier. Ils provoquent des altérations métaboliques étendues et deviennent ainsi de puissants stimulants de l'activité endocrinienne. Nous les diminuons, voire même, les supprimons en apportant au traumatisé un traitement chirurgical. Ce n'est qu'à leur disparition que les mécanismes de défense endocriniens reviennent à l'état de repos permettant ainsi au malade d'entrer dans l'anabolisme, la convalescence et enfin la réhabilitation sociale.

SIZE OF PULMONARY ARTERY IN RHEUMATIC HEART DISEASE WITH ISOLATED MITRAL STENOSIS AND ITS SIGNIFICANCE

Twenty-five consecutive persons with rheumatic heart disease and isolated mitral stenosis were studied by Soloff *et al.* (*Am. J. M. Sc.*, 234: 313, 1957) by a combined technique of cardiac catheterization and sequential biplane stereoscopic venous angiocardiography to determine the diameter of the pulmonary artery and its relationship to that of the aorta, to age, and to various parameters of heart structure and function. The diameter of the aorta is apparently normal and is usually less than that of the pulmonary artery. Only a very low grade relation was found between the diameter of the pulmonary artery and the age of the patient. No significant correlation was found between the diameter of the pulmonary artery and either the volume of the left atrium or the size of the heart. A fair correlation was present between the diameter of the pulmonary artery and the *mean pulmonary wedge pressure*. The correlation was better with the difference in mean pulmonary artery pressure alone. On the basis of 10 cases a good correlation was found between the *diameter of the pulmonary artery and total pulmonary resistance*. The correlation with the pulmonary vascular resistance was of questionable low grade significance. Although there is a significant linear relationship between the diameter of the pulmonary artery and the mean pulmonary artery pressure, for any given pulmonary artery diameter, the mean pulmonary artery pressure may vary widely.

TREATMENT OF THE CHRONIC PARANOID SCHIZOPHRENIC PATIENT*

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THE TREATMENT of chronic paranoid schizophrenia has long been considered one of the most difficult tasks for psychiatrists.

We are presenting a method of treatment which we have found to be more successful than any hitherto reported.

This method consists essentially in the use of prolonged sleep, lasting 30 to 60 days, combined with intensive electroshock therapy. This period of treatment is then followed by a stage of rehabilitation and follow-up therapy on an ambulant basis. This latter is carried on over a two-year period.

OBSERVATIONAL BASIS FOR TREATMENT

1. During the last 20 years we have found frequent occasion to verify Sakel's[1] original observation that a prolonged and severe so-called irreversible coma might have favourable effects in schizophrenic patients who had hitherto failed to respond to any other form of treatment. We have considered that the frequently severe although transient disturbance of brain function is an important factor in the favourable results. This disturbance is shown in terms of severe recent memory deficit, disorientation and impairment of judgment. Similar changes can readily be produced by a combination of sleep and electroshock treatment.

2. In recent years since we re-introduced the use of prolonged sleep with the assistance of chlorpromazine (Largactil)[2] we observed that schizophrenic patients responded well to this form of treatment. Our first attempts to use this treatment were with very excited schizophrenic patients who could not otherwise be managed in an open hospital.

3. Our third observation was that where coma insulin and electroshock were combined in the treatment of particularly difficult schizophrenic patients we got good results.

Thus it was decided to explore the possibility of using prolonged sleep combined with electroshock therapy; within a few months it became apparent that the best results were obtained where there was an extensive breakup of the behavioural patterns consequent upon a transient disturbance of brain function.

The observational basis for the two-year ambulant follow-up was derived from our observations of the use of a five-year follow-up period in patients suffering from recurrent manic depressive attacks as originally suggested by Geoghegan and Stevenson[3] and as carried out by ourselves for the last ten years. The second basis has been our observations of the disorganizing effects of emotional stress and the restoration of function once the disorganizing stress has been removed.[4]

CASE MATERIAL

The patient group in which the effects of this form of therapy was studied consisted of 26 paranoid schizophrenic patients. Of these, 16 had shown symptoms for more than two years. The remaining 10 had shown symptoms for less than two years and were diagnosed as suffering from acute paranoid schizophrenic breakdown. They were included for the purposes of comparison. Of the 26 patients, five were men and 21 were women. The age spread was from 17 to 54.

All patients were examined extensively before treatment. Clinical, biochemical, psychological and electrophysiological examinations were carried out. In addition the family structure and the general socio-economic background from which the patient came was investigated through the social service department. The diagnosis was made on the basis of the accumulated data and as established in joint discussions of the whole clinical team.

After the conclusion of treatment, routine examinations described above were repeated, the clinical team again assessed the degree of recovery which had been achieved, and at the same time plans were made for follow-up and rehabilitation work with each patient.

PROCEDURE

The sleep technique employed is that reported by Azima.[2] The objective of this technique is to produce a prolonged sleeping state resembling the normal as closely as possible. The patient sleeps an average of 20 to 22 hours a day and is wakened three times a day for meals and toilet. The drugs used are chlorpromazine (Largactil) and a combination of three barbiturates: secobarbital (Seconal) is chosen as a short-acting barbiturate, pentobarbital (Nembutal) as one of intermediate duration and phenobarbital or barbital (Veronal) as a long-acting drug. Solid food is given during the first week and from then on semi-solid foods, the minimum caloric intake is 1500 per day and the minimum amount of fluid 2000 c.c. The patients are given extra vitamin B and C parenterally. Posturing of the patients by the nurses is carried out every two hours and carbogen is administered if the respirations become shallow. Five units of globin-zinc insulin are given half an hour before each meal. The sleep is induced gradually and is also terminated gradually. At the end of 10 days, at which time sleep has been established, electroshock is commenced.

The objective of the electroshock therapy is to produce in combination with sleep a condition of confusion which we term complete depatterning. For purposes of identification we recognize three

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stages of depatterning. The first stage is when the patient begins to show serious memory deficits but still has no difficulty in orienting himself with respect to the fact that he is in hospital, that he is there because he is sick, and is still able to recognize at least some of the doctors and nurses and his own family when they visit him.

The second stage is when the patient has lost his spatial and temporal image but is very conscious of the fact and makes repeated attempts to find re-orienting points. He asks, "Where am I?", "how did I get here?" and "what is this place?" In the third stage the feeling that he ought to have a spatial-temporal image is also lost and the patient is now quite smiling and unconcerned. He answers simple questions but does not recognize anyone, has no idea where he is and is not troubled by that fact. He usually shows urinary incontinence and has difficulty in performing quite simple motor skills. During the first stage of depatterning his original delusional ideas are usually still present. During the second stage they are becoming broken up and in the third stage are completely absent, as are all other evidences of his schizophrenic behaviour. To achieve this, electroshock therapy frequently has to be carried out once daily and sometimes in the form of a Page-Russell[5] treatment, namely, the giving of four or five shocks within a period of two or three minutes. The rate of administration of electroshock therapy is set so that complete depatterning is achieved somewhere between the 30th and the 60th day of sleep and after about 30 electroshock treatments.

Once complete depatterning is obtained, it is maintained for five to seven days. The amount of sleep medication is gradually reduced (too rapid reduction of barbiturates may produce convulsions) and the rate of administration of electroshock is reduced to three a week, the Offner apparatus being used.

After about four or five days the patient is able to get up and the phase of rehabilitation is then initiated. Care is taken as far as possible to assign one person to looking after the patient so that he can the more rapidly begin to orient himself, at least with respect to one person. He joins the other patients at meals and as soon as his memory will permit he is referred to the occupational therapy department.

During the period of recovery continuous observations are carried out with respect to any evidence of a recurrence of his schizophrenic behaviour. Should any sign of his previous delusional thinking appear, electroshock is again intensified, the patient being given daily treatments for a few days until the delusional thinking is once more broken up. Ordinarily such relapses do not occur, but in some patients they may recur repeatedly during the period of rehabilitation and on each occasion further electroshock is given until they are broken up again.

Care should be taken to distinguish actual schizophrenic relapses from forms of behavioural disturbance which we have noted in about 25% of our cases at the point of transition from the second to the first stage of depatterning. At this phase in the recovery of the patient—namely, when his attempts to re-establish his space-time image are becoming satisfactory but while there are still severe memory deficits—there may appear states of excitement or depression and states of actual delusional formation, this being in contrast with the placidity and the freedom from any delusional thinking which one finds in the third stage of depatterning. Our experience has shown that this transition period of disturbance of behaviour is best treated conservatively. The patient is usually put on chlorpromazine or reserpine (Serpasil) in moderate doses and is given a great deal of support and reassurance from the start. Such periods of disturbance ordinarily last less than a week and gradually subside as the patient emerges into the first stage of depatterning.

The period of rehabilitation in hospital ordinarily lasts about a month, at the end of which time the patient can be discharged and put on an ambulant follow-up basis. During this period, moreover, through our social service department we plan the patient's rehabilitation on the outside. Preparations are made for the last phase of stabilization and prevention. This generally lasts two years and requires the patient to come to the hospital for one electroshock treatment a week for the first month after discharge and one treatment a month for the next two years. We have repeatedly found that the patients do much better if they remain in the Montreal area and attend the Institute than if they return after discharge to their home city and place themselves under the care of one of our colleagues, being treated in a manner precisely the same as they would be if they had been in Montreal. This interesting observation demonstrates the great significance to the patient of the therapeutic milieu in which he recovered and the need for him to remain in this milieu during the period of stabilization.

The form of psychotherapy which we carry out with these schizophrenic patients during the period of rehabilitation in the hospital and during the two-year follow-up period when they are ambulant is limited to meeting the needs of the patients for support and acceptance and for guidance in their attempts to re-establish themselves in the community and in a job. We do not, save in the rare instances where there are marked neurotic tendencies, undertake any form of depth psychotherapy. Specifically we do not attempt to uncover unconscious motivations. Our efforts are directed rather to building a strong personal relationship between the patient and the therapist. The therapist takes every opportunity to strengthen this relationship, particularly during the period immediately after prolonged sleep when the patient is

attempting to re-orient himself and is gradually recovering from the period of helplessness engendered by his prolonged sleep and electroshock therapy. This relationship constitutes a fixed point of strength and support for a patient and is continued throughout the whole two years, care being exercised to see that, as far as possible, the same therapist is available to the patient. It is important to underscore the fact that the therapist brings to his work not only knowledge and skill but also attitudes. We are increasingly impressed with the fact that the attitudes of the therapist are crucial for the outcome. In dealing with the long-term schizophrenic patient the therapist must have great persistence. He cannot afford to give up easily. He must continually focus his attention and that of his staff and the patient on the gains which have been made, even though for a time they should be small.

During this period of stabilization and prevention outside the hospital, the patient ordinarily works. Some of our patients have married and have had children. Some have shown relapses. Where evidence of relapse is reported to us, the patient is treated again within a few hours or at the most within two days by intensive electroshock therapy on an ambulant basis. We have an arrangement with a nursing organization in the city by which all our ambulant schizophrenic patients are visited once a week, and their relatives or landladies are instructed to get in immediate touch with this nursing organization if there is any evidence of a relapse. This may take the form of moodiness, of sleeplessness, of lack of interest, of impairment of appetite, or of the appearance of thinking difficulties or beginning delusional ideas. We have found that where this happens we are always able to terminate the relapse within two or three days and often within 24 hours by intensive electroshock therapy. In the last two years we have only rarely had to readmit a patient.

RESULTS

It is proposed to report the results of the two groups of paranoid schizophrenic patients separately, namely, those patients having symptoms of more than two years' duration and those patients having symptoms of less than two years' duration. With regard to the first group, which is comprised of 16 patients, the initial results were favourable in that all patients could be discharged home save for one patient who left against advice and has been readmitted for further treatment.

The follow-up results of those discharged were good except in five patients, two of whom refused follow-up care, developing paranoid reactions of such fixity that we could not persuade them to continue. They were nonetheless able to remain outside the hospital. Two others had to be readmitted for further treatment and were later discharged again and have done well. One other had to be readmitted and as indicated above is still under treatment. A number of others have had minor relapses but could be managed on an ambulant basis. Out of all the patients now discharged, paranoid trends were apparent only in the two patients mentioned above as having refused further treatment and in the one patient who had treatment in hospital subsequent to readmission. It should, however, be pointed out at the same time that although most of them are able to lead active lives as housewives and also in other occupations on the outside, some evidence of schizophrenic damage can be seen in the majority of these chronic patients. This takes the form of some blunting of affect, some loss of drive relative to that shown in earlier years.

TABLE I.—RESULTS IN THE TREATMENT OF PARANOID SCHIZOPHRENIC PATIENTS WITH SYMPTOMS OF OVER TWO YEARS' DURATION

Number of patients	16
Number discharged	16
Number readmitted	3
Number re-discharged	2
Number still in hospital	1
Number refusing follow-up treatment but still ambulant	2

Those in the group with symptoms of less than two years' duration have all been discharged and the results are also good, indeed more favourable than in those with symptoms of over two years' duration. None of them have had to be readmitted. Occasional relapses have been seen but these have been managed quite successfully on an ambulant basis. The evidence of lasting schizophrenic damage in the form of blunting of affect, or reduction in drive and initiative, is rarely apparent in this group of short-term paranoid cases.

TABLE II.—RESULTS IN THE TREATMENT OF PARANOID SCHIZOPHRENIC PATIENTS WITH SYMPTOMS OF LESS THAN TWO YEARS' DURATION

Number of patients	10
Number discharged	10
Number readmitted	0

DISCUSSION

Earlier in this paper we presented the observational basis for the development of this technique. We now wish to present the theoretic basis. Our working theories or premises are three in number:

1. That schizophrenia represents a biological process which can be arrested but which tends, particularly when of any intensity or duration, to leave behind permanent damage.

2. That recovery consists primarily in: (a) halting the process, and (b) a reorganization of the individual which results in a short-circuiting or inactivation of the damaged area but which does not result in an abolition of the established damage.

3. That a considerable proportion of schizophrenic relapses, though certainly not all, constitute not a reactivation of the process but a breakdown

of the reorganization of the individual, usually under emotional stress.

Turning now to deal with the premises in more detail we may say that we have found chemical and physical therapies to be the only satisfactory means of halting the schizophrenic process. The objective of our initial intensive physical and chemical therapy is two-fold, first to bring the process to an end and second to break up completely, through the procedure of depatterning already described, the ongoing structure of the behavioural patterns of the individual. This results in breaking up at the same time the pathological schizophrenic thinking and general symptomatology.

Turning to the second premise, namely, that recovery requires reorganization, we wish again to emphasize the need to break up old pathological patterns before the new ones can be re-established. We may also indicate the value of psychotherapy at this point. The psychotherapy is, as indicated, supportive and also directive in so far as the pressures of the social setting are brought to bear on the patient in an attempt to get him to establish acceptable patterns of behaviour.

Numerous reports in the literature indicate that where a patient has made a good clinical recovery psychological tests may well show the same amount of schizophrenic damage as before. We see this as supporting the premise which we have put forward, namely, that recovery consists not in repair of damaged aspects of the individual's personality but in a rearrangement. The damaged parts are, as it were, bypassed or omitted from the key areas of the patient's new organization. We are further of the opinion that every individual possesses reserve capacities—alternative ways of managing reality and latent assets—which can be called upon and woven into the new organization of the self. This means, of course, that the damaged areas which have suffered schizophrenic damage are still present within the individual and that there always remains the possibility of a breakdown in the new organization and a return to the old but still existing patterns of schizophrenic behaviour.

This takes us to the third premise, namely, that under the impact particularly of emotional stress the new organization may break down, disorganization[4] may occur and the previous schizophrenic patterning may reappear. It is to protect the patient against the possibility that the earliest evidences of damage due to stress might not be noticed and hence that the patient would begin to pass into disorganization that our plan of treatment requires weekly visits by the nursing organization and monthly interviews with the therapist, together with a monthly electroshock treatment over the two-year period. When relapses do, nonetheless, occur they are treated on an ambulant basis; the patient is seen if necessary daily for three or four days and receives an electroshock treatment daily on an ambulant basis. Under these circumstances we have almost invariably succeeded in bringing the relapse to an end within a few days.

SUMMARY

The results of combined prolonged sleep and intensive electroshock treatment with subsequent rehabilitation and follow-up ambulant therapy in chronic paranoid schizophrenic patients have been presented.

The group of patients consists of 16 chronic paranoid patients having had symptoms of two or more years' duration contrasted with a group of 10 paranoid schizophrenic patients with symptoms of less than two years' duration.

Three of the long-term cases have been readmitted and two of these have been subsequently discharged. One is still in hospital undergoing re-treatment. The longest period of follow-up subsequent to discharge is two years.

Two of the long-term patients have broken treatment and have again showed paranoid symptomatology but remain outside the hospital.

Minor relapses have occurred in several of the patients, in both the long-term and short-term cases, but these have been managed successfully on an ambulant basis. None of the short-term cases has had to be readmitted.

In the long-term cases some residual evidence of schizophrenia can be seen. This takes the form of reduction in drive and blunting of affect. In only three of the long-term cases (two who have broken therapy and the one who has been readmitted) and in none of the short-term cases is there any evidence of paranoid thinking.

Our primary purpose in this presentation is to show that our therapeutic procedures have advanced to the point where it is now possible for schizophrenic patients, even when suffering from the most severe forms of the illness, to be passed through a phase of intensive treatment followed by long-term rehabilitation measures and thereby be enabled to live, and in many instances work, outside the hospital.

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RÉSUMÉ

Les auteurs de cet article ont récemment fait l'essai d'un traitement combiné de sommeil prolongé et de sismothérapie intense chez des schizophrènes paranoïdes chroniques, réhabilités par la suite, et suivis à la clinique externe. La présente série comprenait un groupe de 16 malades dont les symptômes remontaient à au moins deux ans et que l'on a comparé à un autre groupe de dix malades dont les symptômes étaient d'origine plus récente. Trois malades du premier groupe durent être hospitalisés de nouveau, mais deux d'entre eux ont depuis reçu leur congé. Le troisième est encore sous traitement. Ces malades furent vus pendant deux ans à différents intervalles après leur sortie de l'hôpital. Deux autres malades du premier groupe abandonnèrent le traitement et retombèrent sous l'effet de leur symptomatologie paranoïde, mais sans toutefois revenir à l'hôpital. Certaines recrudescences de peu d'importance furent notées chez plusieurs malades des deux groupes et toutes répondirent au traitement à la clinique externe. Aucun malade du deuxième groupe n'eut à être hospitalisé de nouveau. On peut encore déceler

certains signes de schizophrénie chez les malades du premier groupe dont la symptomatologie remontait à plus de deux ans. Ces signes se manifestent par un dynamisme réduit et un émoussement de l'affectivité. Dans seulement trois des cas du premier groupe (ceux qui abandonnèrent le traitement et celui qui dut revenir à l'hôpital), trouve-t-on encore des signes d'interprétation paranoïde; tous les malades du deuxième groupe en sont exempts. Le but que se proposaient les auteurs de cette présentation est de montrer que grâce aux procédés thérapeutiques actuels, il est possible que des schizophrènes, même s'ils sont affectés de la forme la plus grave de cette maladie, peuvent subir une phase de traitement intensif suivie de mesures de réhabilitation à longue échéance pour en arriver enfin à vivre et même souvent à travailler ailleurs que dans un milieu hospitalier.

THE CLINICAL AND METABOLIC EFFECTS OF GLUCAGON*

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SHORTLY AFTER the discovery of insulin it was noted that the intravenous administration of crude preparations of this hormone produced a transient hyperglycæmia before the characteristic hypoglycæmic action of insulin occurred. On the basis of these observations Murlin[1] suggested that pancreatic extracts contained, in addition to insulin, a hyperglycæmic substance which he named glucagon.‡ Burger and Brandt[2] were among the first to study the physiological effects of glucagon. They worked with crude preparations of this material. Partial purification of glucagon was achieved by Sutherland *et al.*[3] and the material was finally isolated in crystalline form by Staub and co-workers[4] in 1953. Glucagon has been chemically characterized as a single polypeptide chain of low molecular weight.[5]

Most studies dealing with the metabolic effects of glucagon in humans have been carried out over a short period of time. The only consistent effect obtained has been the rapid breakdown of liver glycogen which raises the blood sugar level quickly but temporarily.

Recently Salter, Davidson and Best[6] have shown that if glucagon is administered to experimental animals by multiple daily injections, or in a medium that delays absorption, sustained hyperglycæmia and increased excretion of urea nitrogen results. The net effect on protein metabolism is similar to that induced by the glucocorticoid hormones.

It was this similarity to cortisone that led Salter to suggest the cautious administration of glucagon to patients with rheumatoid arthritis and allied disorders to determine whether long-acting glucagon would lead to protein depletion in humans and whether this action would be accompanied by an anti-inflammatory effect.

METHODS AND PROCEDURES

We have given crystalline glucagon by slow intravenous drip to eight patients with rheumatoid arthritis and allied disorders. The dose ranged from 2.5 mg. to 25 mg. a day. It was usually dissolved in 500 c.c. of normal saline. The infusion was begun one hour before breakfast and allowed to run in over a period of 10 hours. The longest uninterrupted course was four days. Some patients were given intramuscular and hypodermic injections so that the effectiveness of these different methods of administration might be compared. This report deals chiefly with the effects of intravenous administration of glucagon.

RESULTS AND COMMENT

Clinical Effects:

(a) Nausea was common to all of these patients. In three of them metabolic balance studies had to be discontinued because of vomiting. Although nausea was sometimes noted when the blood sugar was rising rapidly, it also occurred when blood sugar was normal or low. There have been other reports that glucagon has an inhibitory effect on gastric and intestinal smooth muscle.[7, 8]

(b) Anti-inflammatory action. Our patients could be divided into two groups: Five of them had active synovial inflammation in several joints; three had long-standing disease with gross destruction of articular surfaces and irreversible deformity.

In all of the patients of the first group there was considerable reduction in pain and stiffness in the joints, apparent two or three days after glucagon was started. Two patients with fluid in knee joints showed a measurable decrease in the size of the effusions. The erythrocyte sedimentation rate did not change significantly although there was a reduction of over 100 mg. in the plasma fibrinogen level in one patient. Relapse occurred in all of these patients a few days to a few weeks after glucagon was discontinued.

None of the patients with chronic destructive arthritis had more than slight symptomatic benefit from the administration of glucagon even though the metabolic effects obtained were equivalent to those observed in patients of the first group.

Metabolic Effects:

(a) *Carbohydrate Metabolism*

(i) Hyperglycæmia: In all of the patients the blood sugar rose before breakfast at 9:00 a.m. under the influence of glucagon given at 8:00 a.m.

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‡Also known as the hyperglycæmic-glycogenolytic factor.

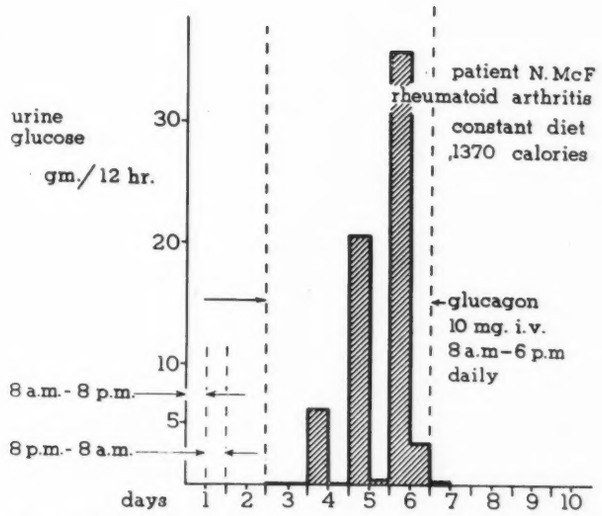

Fig. 1.—Increasing glucosuria from constant dose of glucagon.

intravenously, intramuscularly or hypodermically. The rise in blood sugar level, in the first hour after intravenous glucagon was begun, varied from 40 to 190 mg. per 100 ml. In some patients the blood sugar level remained elevated as long as the hormone was being infused. Mid-afternoon values of 200 to 300 mg. per 100 ml. were often found. The hyperglycæmic response usually increased on successive days. In two patients, glucosuria increased from negligible quantities in the first 12 to 24 hours to as much as 40 g. during the third or fourth day. Fig. 1 shows the increase in glucosuria resulting from the daily infusion of a constant dose of glucagon. When glucosuria appeared, it was found almost entirely during the period of administration of glucagon. Two patients showed no glucosuria.

(ii) Hypoglycæmia: Unless glucagon was continued through the night, the fasting blood sugar level taken the next morning was either normal or in the hypoglycæmic range. The hypoglycæmia

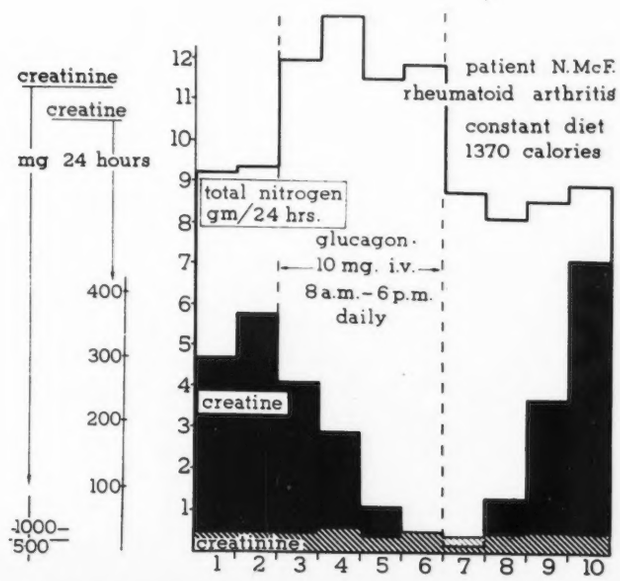

Fig. 2.—Effect of glucagon on urinary nitrogen.

sometimes seen after administration of glucagon is probably associated with increased insulin secretion stimulated by the initial high blood sugar levels.

(b) *Effect on Nitrogen Balance*

Satisfactory nitrogen balance studies were carried out in four patients. In all of these patients it was shown that the intravenous administration of glucagon in doses of 5 mg. or more in 10 hours produced a definite increase in the urinary excretion of total nitrogen, beginning on the first day and lasting as long as it was given. The effect of glucagon on the urinary excretion of total nitrogen, creatinine and creatine is shown in Fig. 2. The creatinine levels did not vary much. We interpret their constancy as evidence of accurate 24-hour collections.

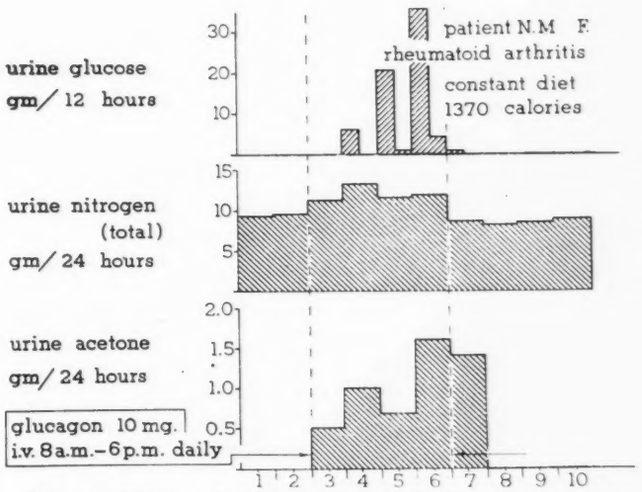

Fig. 3.—Effects of intravenous glucagon: increased excretion of glucose, total nitrogen and acetone.

The effect on creatine excretion in three patients in whom it was measured was striking. After a day or two on glucagon without much change, creatinuria decreased to negligible quantities. This is strong evidence against the adrenal glucocorticoids playing more than a permissive role in the anti-inflammatory and catabolic actions of glucagon, since increased creatine excretion is a characteristic effect of cortisone and its analogues. There was no significant change in the urinary excretion of amino nitrogen.

(c) *Effect of Fat Metabolism*

Ketosis was observed in six of these patients. It occurred when the blood sugar was low, normal or high. In one patient the CO_2 combining power fell to 22 volumes per cent on a day when she was excreting six grams of acetone in the urine. A composite chart of the effect of glucagon on the urinary excretion of glucose, total nitrogen and acetone is shown in Fig. 3. Ketosis and increased excretion of total nitrogen occurred before glucosuria was observed. Ketonuria continued a day after glucagon was discontinued.

(d) *Adrenal Cortical Stimulation*

Glucagon increased the urinary excretion of 17-hydroxycorticoids above control levels in six patients. In only one patient was the level raised above 10 mg. per 24 hours, which is the upper limit of the normal range established for the method used in Dr. Laidlaw's laboratory where the determinations were done.[9]

There was no suppression of circulating eosinophils in three patients in whom they were counted.

DISCUSSION

Sutherland and Cori[10, 11] have shown that glucagon causes rapid hepatic glycogenolysis and subsequent hyperglycæmia by activating the enzyme phosphorylase. However, glucagon appears to do much more than facilitate the breakdown of liver glycogen. It is a potent catabolic agent, capable of inducing a significant negative nitrogen balance by causing a marked increase in the degradation of amino acids. The residues arising from the deamination of the amino acids are synthesized into glucose. Thus the sustained hyperglycæmia produced by glucagon appears to be the result of an increased production of new glucose from amino acids as well as increased hepatic glycogenolysis.[6] The former process is believed to play the most important role in the genesis of the diabetic-like state.

Ketosis and ketonuria of the intensity observed during these investigations may be explained only in part by catabolism of ketogenic amino acids. It seems likely that an alteration in the metabolism of fatty acids also contributes to the increased concentration of ketone bodies.

It has been observed that laboratory animals treated with small amounts of glucagon exhibit a negative nitrogen balance without hyperglycæmia.[12] This was also observed in one of our patients who showed ketosis and a negative nitrogen balance with normal blood sugar concentrations. In such a case the overproduction of glucose by the liver is probably followed by an increase in the secretion of insulin sufficient to maintain the blood sugar levels within normal limits by accelerating the disposal of the glucose in the peripheral tissues. There is no convincing evidence that glucagon has any *direct* effect on the extrahepatic utilization of carbohydrate.[13-16]

It is not possible, on the basis of the data at present available, to explain the acceleration of amino acid catabolism or the reduction in creatinuria that occurs when glucagon is administered. It is suggested, however, that if acute inflammatory processes require active protein synthesis, then glucagon may reduce inflammation by limiting the anabolism of protein.

SUMMARY

The prolonged administration of glucagon has been shown to lead to an increased excretion of total nitrogen, ketosis, and a decreased excretion of creatine. Transient hyperglycæmia always occurred, and sustained elevation of blood sugar levels was usual but less constant.

The administration of glucagon was followed by temporary relief of acute inflammation in several patients with rheumatoid arthritis and related disorders. The side effects induced were extreme nausea, hyperglycæmia and ketosis.

The benefits derived from the short-term administration of glucagon in the dosage used were not great enough to outweigh the distressing side effects produced. The striking metabolic changes observed and their association with reduction in the acute inflammatory process are, however, of great interest. It is possible that further experimental study of such changes may lead to a better understanding of the mechanism of inflammation.

The authors wish to express their indebtedness to Drs. A. G. Gornall and J. C. Laidlaw, who generously contributed their advice and laboratory facilities. Eli Lilly & Company kindly made available an ample supply of crystalline glucagon.

The metabolic studies were conducted in the Clinical Investigation Units at Sunnybrook D.V.A. Hospital and Toronto General Hospital.

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RÉSUMÉ

L'administration prolongée de glucagon provoque de la cétose, une augmentation dans l'excrétion de l'azote total mais une diminution dans celle de la créatine. Une hyperglycémie transitoire se produit constamment et souvent même elle peut être soutenue. L'administration de glucagon fut suivie d'un soulagement temporaire de l'inflammation aiguë chez plusieurs malades atteints de polyarthrite chronique évolutive, ou de troubles associés. Les incidents du traitement comprirent de fortes nausées, de l'hyperglycémie et de la cétose. Les avantages que procure l'administration brève de glucagon dans ces cas ne sont pas suffisants pour compenser les effets fâcheux qui s'y rattachent. Les altérations métaboliques que l'on observa relatives à l'apaisement du processus inflammatoire n'en soulèvent pas moins un grand intérêt. L'étude expérimentale de ces altérations pourrait contribuer à une meilleure connaissance du mécanisme de l'inflammation.

THE TREATMENT OF HEPATOLENTICULAR DEGENERATION WITH PENICILLAMINE, WITH REPORT OF TWO CASES*

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J. E. BOULDING, M.D., C.M.† and
R. A. BAKER, M.S.A., *Essondale, B.C.*

IN THE NEUROLOGICAL LITERATURE of the late 19th and early 20th century, a number of cases of nervous disorder occurring in young people were described in which autopsy findings of hepatic cirrhosis with cerebral lesions were noted.

No clinical inference was drawn from these casual and scattered observations till 1911, when S. A. Kinnier Wilson established that these cases constituted a specific nosological entity. He defined this descriptively as "progressive lenticular degeneration, a familial nervous disorder associated with cirrhosis of the liver". This name was later contracted to the current form, "hepatolenticular degeneration".

According to Wilson's first definition it is: "A disorder which occurs in young people, which is often familial but not congenital nor hereditary; it is essentially and chiefly a disease of the extrapyramidal motor system and is characterized by involuntary movements usually of the nature of tremor, dysarthria, muscular weakness, spasticity and contractures, with progressive emaciation; and these may be associated with emotionalism and certain symptoms of a mental nature. It is progressive and, after a longer or shorter period, fatal. Pathologically it is characterized by bilateral degeneration of the lenticular nuclei, and in addition, cirrhosis of the liver is constantly found, the latter morbid condition rarely if ever giving rise to symptoms during the life of the patient."[1]

Curious rings of golden brown pigmentation in Descemet's membrane near the outer margin of the cornea were noted by Kayser and Fleischer between 1901 and 1911 while they were studying a disease known as "pseudosclerosis" but later shown to be a more slowly progressive form of hepatolenticular degeneration. Wilson was apparently unaware of this pigment deposit in his cases. It has been observed in nearly all subsequently studied cases. Conversely, it has never been seen in any other neurological or systemic disorder, so that the presence of the Kayser-Fleischer ring is now regarded as a pathognomonic sign of Wilson's disease.

A historical milestone in the understanding of this disease was reached in 1930 when two German workers (Horowitz and Luethy) noted an increased concentration of copper in the liver and brain of patients with Wilson's disease. This finding was later confirmed by Glazebrook in 1945.

It is now well established that a central feature of this disorder is a positive copper balance,[2] with a resulting accumulation of copper in all the tissues of the body and consequent intoxication of the cells of these various tissues, particularly the brain and the liver. A normal diet contains over two mg. of copper per day. Usually this copper is almost entirely excreted in the fæces. Patients with hepatolenticular degeneration, however, absorb as much as 50% of the dietary intake. They are in positive balance to the extent of one mg. a day or more. It is probable that the copper content of the soil in areas where the patients live determines the quantity of the copper ingested and the rate of the development of the disease. Whether this positive copper balance is primary or secondary remains to be solved. A deficiency of cœruloplasmin has been noted as a further manifestation of this disease. Cœruloplasmin, a blue alpha globulin containing eight atoms of copper per molecule, has oxidase activity. All cases of Wilson's disease which have been studied show a very marked reduction of the blood level of this enzyme. The enzyme deficiency is felt by some authors to be fundamental in the disease and by others to be a secondary manifestation.

In recent years it has appeared increasingly probable that the disease is due to a genetic disorder. A high rate of the disease amongst siblings with an absence of the disorder in parents coupled with a high consanguinity rate makes it seem likely that the genetic disorder is a recessive characteristic. The heterozygote does not show the disorder but the homozygote may. It can be assumed that one recessive gene from each parent is necessary for the clinical expression of Wilson's disease to be possible.

Our observations are based on two brothers of a family of four children. The remaining two are girls, who seem to be unaffected. There is no family history of any neurological disorder but information is scanty on the maternal side.

James, the older boy, was admitted to the Crease Clinic at the age of 13 years, in May 1951. His parents had found him uncooperative and difficult to manage. This formerly handy farmer's boy had gradually become clumsy and awkward in his movements, so that he would often "soil himself" while eating. He exhibited tremors of his face and hands. At times his hands assumed grotesque positions. His speech became indistinct and he drooled saliva continuously from his open mouth. This led his classmates at school to make fun of him and to nickname him "Slobber". In face of these difficulties, the patient tended to avoid the company of his playmates and became increasingly more solitary and withdrawn. These symptoms appeared gradually but advanced steadily during the course of a year. They seemed to have come on after an acute illness in May 1950, when he had suffered for two weeks from diarrhœa, vomiting and mild jaundice.

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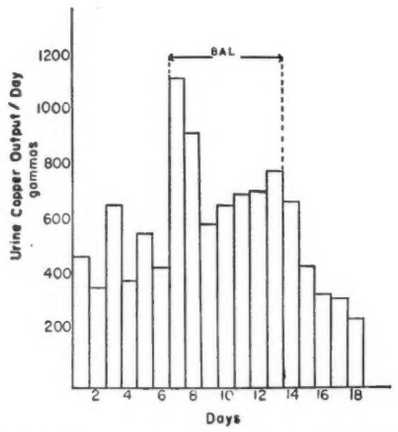

Fig. 1.—Initial response to B.A.L. (2,3-dimercaptopropanol), 150 mg. twice a day intramuscularly.

The clinical picture was characterized by a generalized slowing of all muscular movements. His face was blank and expressionless. His voice had a monotonous, uniform pitch and his articulation was faulty. While he occasionally showed a coarse tremor of the lips, tongue and upper extremities, the most striking presenting sign was muscular rigidity. The fingers of both hands were flexed at the metacarpophalangeal joints and extended at the interphalangeal joints. He walked on a wide base and lacked the normal accessory arm movements. He exhibited a marked slowing of muscular relaxation after voluntary contraction. Fine alternating movements with his hands and fingers were poorly executed.

A fairly broad golden brown pigmented ring around the outer margin of his cornea was seen. His liver was hard and enlarged, and extended 1½ in. (3.8 cm.) below the right costal margin, and the spleen was readily palpable.

While investigations were in progress, the patient suffered a catastrophic hæmorrhage from a ruptured œsophageal varix and died, in spite of energetic therapeutic measures, within a few hours.

It has been previously pointed out that a remarkable consistency exists in the age and manner of onset of this disease. This was strikingly borne out by our two patients. A year after James's death, his parents contacted one of us, fearing that their second son, Glen, showed signs of this same disease. Glen was then 13 years of age. Like his older brother, he had suffered from a severe gastric upset when he was 10. He had had diarrhœa and vomiting for a week and seemed generally out of sorts for the ensuing six weeks, during which time he lacked "pep" and ambition. Gradually, preceding admission, it had become increasingly difficult for him to engage in such activities as baseball or to carry out any other movements which demanded quick and fluent muscular adjustments. Whereas formerly he had been a lively lad, he began to tire readily and to an extreme degree. On admission in June 1952 his speech was muffled and thick. He had difficulty in initiating movements. His lower jaw dropped and saliva started to drool from his half-open mouth. He became quite pale, and lost a great deal of weight. He had crescentic depositions of reddish-brown pigment in the upper and lower margins of his corneas. His liver, but not his spleen, was palpable. Estimation of his urinary copper output disclosed increased renal excretion of copper and aminoaciduria.

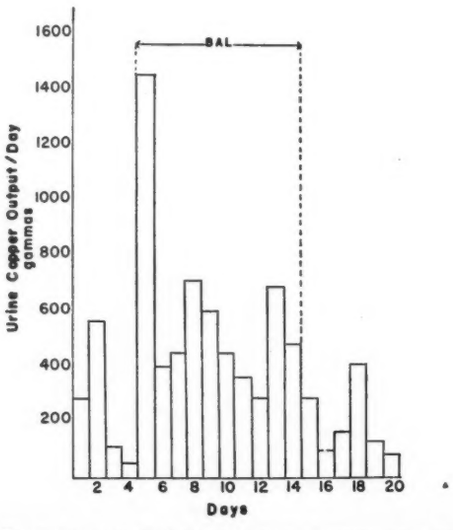

Fig. 2.—Response to B.A.L. after one year on the drug. Treatment 5 days out of 10 with 150 mg. twice a day.

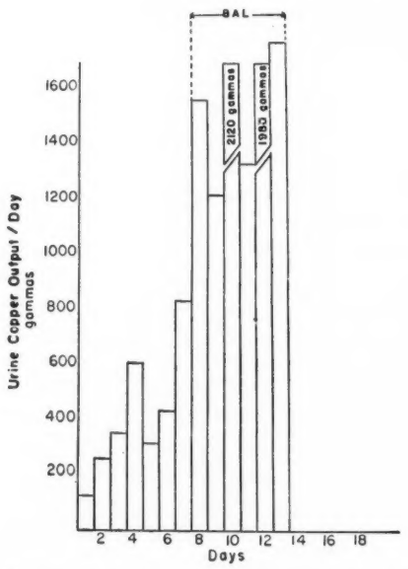

Fig. 3.—Response to B.A.L. after some weeks off treatment. Note the pronounced high response after rest.

After a course of twice-daily injections of 1.5 mg. dimercaprol (B.A.L.) per kg. at monthly intervals, he gained 15 lb. and he did not become fatigued so readily. The stiffness of his fingers was less pronounced and his drooling was diminished. His liver was palpable 1½ in. (3.8 cm.) below the right costal margin.

He was discharged and the same treatment regimen was carried out at home under the supervision of his local physician. Six months later, in April 1953, his condition had deteriorated. The slurring of his speech had increased. He again became tired very readily and was generally listless. Although he had grown 1½ in. (3.8 cm.), his weight was down. After readmission he was found to have moderate microcytic anæmia, but sternal marrow puncture did not disclose any abnormalities. After a month in hospital his general and neurological status showed a slight improvement. However, towards the end of 1953, his muscular rigidity increased and became more pronounced in the right than in the left upper extremity.

Early in 1955 it became obvious that Glen's disorder was relentlessly marching on and that in spite of the intense treatment program of a high protein diet, 20 mg. of potassium sulphide three times a day

with meals, five-day courses of B.A.L. every 10th day combined with intravenous calcium versenate, it was not possible to keep him in negative copper balance. He always lost weight while he was at home and complained of increasing fatigability and heightened susceptibility to upper respiratory infection. His dysarthria became more obvious and his muscular rigidity increased to the point where writing was becoming very difficult. The tremor previously in his jaw and tongue also now involved his right hand.

By October 1956 his disabilities assumed catastrophic proportions. He was barely able to walk. His gait became so ataxic that he could only stagger for a few steps, and he finally became bedridden. His speech was almost unintelligible, so that he could communicate only by means of a spelling chart. The tremor of his upper extremities involved the shoulder musculature and resulted in the gross alternating abduction and adduction picturesquely described as *Fluegelschlagen* (flapping). His general feeling of

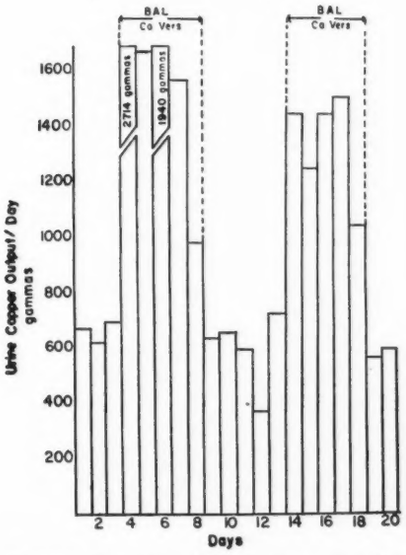

Fig. 4.—Copper diuresis when B.A.L. was first combined with calcium versenate (calcium disodium ethylenediaminetetracetic acid), 1 gram daily in 200 ml. of 5% glucose as a slow intravenous drip. Treatment for 5 days followed by 5 days' rest.

malaise was accentuated by insidious vomiting and diarrhœa. His previously enlarged liver was no longer palpable. To the list of aberrant results of liver function tests, a severely depressed prothrombin time was added, which did not respond to the conventional countermeasures. The import of this sign was the more ominous in view of his brother's sudden death from a ruptured œsophageal varix.

On December 1, 1956, treatment with penicillamine (dimethylcystine) was started. At this time the patient was almost moribund. His family was informed that he was unlikely to live until Christmas. He was bedridden, anarthric and unable to help himself in any way. He suffered from bronchial pneumonia with a high fever, though on continuous penicillin by mouth, 1.0 g. daily. When penicillamine was administered according to the regimen of Walsh[3,4], the response was dramatic. The urinary excretion of copper reached values heretofore unknown in our laboratory and the clinical course showed a steady improvement. By Christmas-time the boy could go out for the day in a wheelchair. His tremor and rigidity were lessened, and

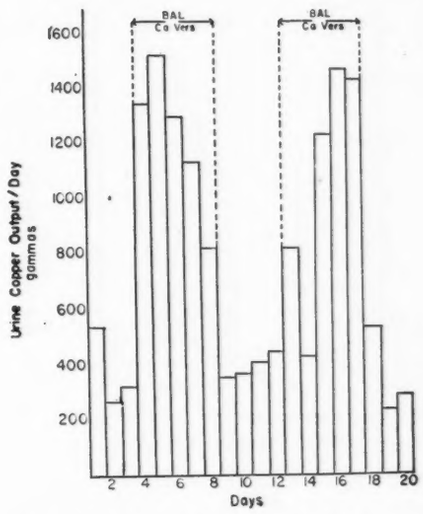

Fig. 5.—Response to B.A.L. and calcium versenate after one year on the combination.

a few words of his speech could be understood. By the middle of January, the patient was out of bed all day. He had gained 20 lb. in weight, was able to feed himself although very messily, and could walk for a few yards. By the middle of February, his speech had become quite clear; he could dress himself but not do the buttons. By April he could walk several hundred yards and was attending school for an hour a day. The drooling of saliva which had been distressing even with Cogentin (benztropine methanesulfonate) 2 mg. four times a day had ceased by this time and Cogentin was discontinued. The patient was easily fatigued. In May, the patient was able to write his first name so that it could be recognized, for the first time in three years. He had gained 30 lb. in weight. Daily 24-hour urinary copper determinations were done and it was noted that the patient remained throughout in negative copper balance. Doubling and quadrupling the dose of penicillamine had no apparent affect on copper excretion. For four months after the institution of penicillamine treatment the patient's prothrombin time remained depressed in

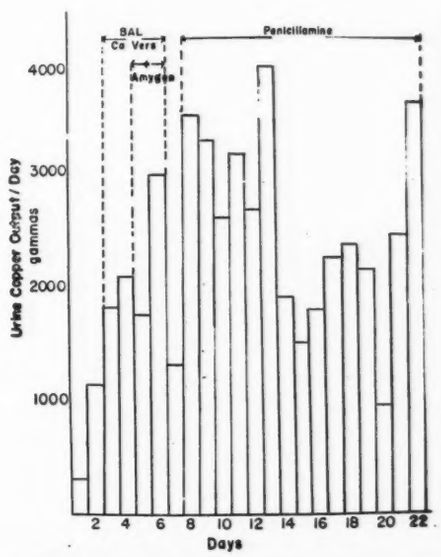

Fig. 6.—Response to penicillamine compared with all other therapeutic measures combined when penicillamine first was used. The dose was of 0.3 gram ½ hour before meals 3 times a day. Treatment was continuous without any days of rest.

the range of 20% of normal. After this it slowly rose to near normal levels.

At the time of writing, August 1957, the patient is continuing to improve. He has gained 40 lb. but has not increased in height. His speech is normal for short lengths of time. His gait is unremarkable. Fatigue remains a problem. A walk of about 200 yards is all he can manage. From time to time the patient becomes depressed for no apparent reason. The sensorium is clear, as it has always seemed to be. He has received average to high marks in his school work. The Kayser-Fleischer rings are now seen only with a slit lamp.

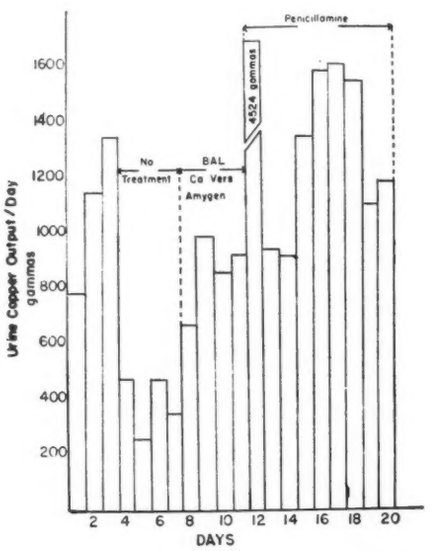

Fig. 7.—Comparative response after 6 months on penicillamine. Some of the variation in these daily copper estimations is due to the difficulty of collection of the 24-hour urine specimens.

The diet is restricted in copper content to about one-half the normal amount. He drinks only distilled water. At the present time we contemplate keeping the patient on pencillamine 300 mg. three times a day, 30 minutes before meals, indefinitely.

The complications of penicillamine therapy appear negligible. As a precaution against the depletion of the body of essential metals which might be chelated and excreted along with the copper, the patient has been given a mineral supplement. It is given Saturdays and Sundays in a dose of: 5 mg. of calcium carbonate, 5 mg. ferrous sulphate, 1.25 mg. magnesium chloride, 0.05 mg. cobalt nitrate (crystalline), and 0.05 mg. zinc sulphate (crystalline), twice daily, after meals.

The penicillamine used was made from penicillin. We have also studied the effect of L-penicillamine and racemic or DL-penicillamine, all as the hydrochloride. As regards the copper output in the urine, these three substances are apparently identical. Wilson and Du Vigneaud[5] report that L-penicillamine is toxic to rats, producing fits and convulsions, while D-penicillamine is harmless. These symptoms were not noted in this case and the patient continued to improve while on the L-preparation. His copper excretion remained at a uniformly high level of from 2.5 to 4 mg. per day while he received 5 grams of L-penicillamine in six days.

SUMMARY

A discussion of hepatolenticular degeneration is presented. Two cases are reported, one of which has been under treatment for four years. Treatment of this case first with B.A.L. and then with calcium versenate, is described and contrasted with the more successful treatment with penicillamine. The better results with penicillamine are felt to be due to its ability to cause a greater diuresis of copper than either or both the other agents. The steady improvement of the case treated with penicillamine paralleled his degree of negative copper balance. It is considered that, as far as this case goes, penicillamine is a superior therapeutic agent for the treatment of hepatolenticular degeneration than previously available chelating agents. It has the additional advantage of being effective orally.

Studies of the different optical isomers of penicillamine are reported which show that they are identical with regard to their ability to cause a copper diuresis in Wilson's disease.

ADDENDUM

One of us has had the opportunity to treat a second case of hepatolenticular degeneration with penicillamine since this paper was submitted. It is too early to comment on the clinical course but it is possible to say that the copper diuresis has been very satisfactory.

The authors wish to thank their many colleagues who aided this study, particularly Dr. C. N. Brown, Medical Adviser to the Distillers Co. (Biochemicals) Ltd., who donated several hundred grams of D-penicillamine hydrochloride; Dr. J. W. Cornforth of the National Institute of Medical Research, Mill Hill, London, for the gift of DL-N-formylisopropylidene: penicillamine, from which Dr. Morin Atchison prepared DL-penicillamine for us; Dr. A. M. Gee, Director of Mental Health Services, Province of British Columbia, for his co-operation; and the secretarial staff of the Provincial Mental Hospital, Essondale, B.C., for their aid in preparing the manuscript.

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DIFFERENTIAL DIAGNOSIS OF VESICOVAGINAL AND URETEROVAGINAL FISTULA

For the differential diagnosis of these two types of fistulas, a small vaginal pack moistened with weak ammonium hydroxide or sodium bicarbonate solution is inserted in the vagina. An injection of 100 c.c. of methylene blue is made through a catheter into the bladder. The catheter is then removed without spilling any of the dye into the vaginal vault. An injection of 1 c.c. (6.0 mg.) of phenolsulfone-phthalein is administered intravenously (P.S.P. is excreted by the kidneys and when collected in an alkaline medium produces a red colour.) The vaginal pack is removed in 30 minutes. If the pack is blue, a vesicovaginal fistula is presumed to be present; if the pack is red, a ureterovaginal fistula.—D. H. Callahan and R. E. McKendry, *Quart. Bull. Northwestern U. M. School*, 31: 193, 1957.

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Jan. 15, 1958, vol. 78

THE B.C.G. STRAIN: NEWER KNOWLEDGE OF ITS BIOLOGY AND IDENTIFICATION

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INTRODUCTION

IN DECEMBER 1953, the Expert Committee on Tuberculosis of the World Health Organization met in Copenhagen to study certain problems arising in B.C.G. immunization in different parts of the world. One of the main conclusions of the report, which one of us wrote as a convener, was: "The Committee has examined the question of whether there really exist differences between B.C.G. strains used for the preparation of vaccine in different parts of the world. It has been shown through the use of vaccines prepared in several laboratories that notable differences exist in the allergic properties as well as in the intensity of induced lymph node reactions. These variations are particularly evident in immunization by the oral route, especially when comparison is made of the results obtained with the B.C.G. strain utilized for the preparation of vaccine in several laboratories of South America and those observed with the strains used in a few other laboratories. The Committee has deemed new studies necessary to determine whether these variations were attributable to differences in the methods of preparation and administration of the vaccine and in some characteristics of the vaccinated population, or whether they arise from biological differences between the strains used."

Important differences between vaccines and even strains of certain laboratories have recently been described in several publications. Unless this situation is clarified immediately, the future of vaccination against tuberculosis may suffer some inconvenience. For this purpose the Sub-Committee on B.C.G. of the International Union against Tuberculosis sent a questionnaire to all known B.C.G. laboratories, in 1956. The aim of the Sub-Committee was to compare the different methods of culturing the strain of B.C.G. and of preparing the vaccine, evaluate the importance of existing differences and determine their ultimate influence upon the use of B.C.G. Most of the laboratories (39 out of 48) replied to the questionnaire and the Sub-Committee decided to hold an International Technical Conference on B.C.G., in Geneva (October 1956). The senior author was appointed rapporteur, with the responsibility of analyzing problems relative to strains of B.C.G. He completed the above survey by correspondence with 40 of the main B.C.G. laboratories in the world. Three other rapporteurs—Dr. K. S. Ranganathan of Madras, Dr. Pedro Domingo of Havana, and Dr. Hideo Kumabe of Tokyo—were made responsible for drawing up similar reports on the preparation of vaccinal suspension, the control of this suspension and the lyophilization of B.C.G. respectively.

Delegates from 39 B.C.G. laboratories in all parts of the world attended this conference. International health agencies such as the World Health Organization, the International Children's Centre, and the International Association of Microbiologists sent observers.

The influence of culture media and techniques for maintenance of the original B.C.G. strain has already been discussed in our general biological study of the strain. This paper, which also includes notes on the control of the strain, is to be published in book form. The present article deals with the conclusions we have reached in our survey of the subject.

I. STABILITY VS. VARIATION OF THE STRAIN OF B.C.G.

It is fundamentally important to determine whether the original strain of B.C.G. from the Pasteur Institute has been modified by the influence of culture media or by maintenance techniques either in its laboratory of origin or in any of the institutes where it is used for the preparation of the vaccine or for experimental purposes.

The opinion of experts on B.C.G. production about the homogeneity or the stability of B.C.G. does not always agree with that of research workers or clinicians. One of the causes of this misunderstanding may be the inaccuracy of the conventional methods for research in tuberculosis. Recent advances in this field may throw some light on the problem.

A Genetic Approach

Since bacterial variability is related to genetics, the vocabulary of this section pertains to that branch of biology. Variations in the genotype (stable and hereditary mutations) must be distinguished from those of the phenotype which are conditioned by the environment and are reversible. According to genetic theory, the B.C.G. strain represents a heterogenous population made up of mother-cells and of variants in different proportions. The phenotype which results would have acquired a certain stability from the onset and, through special maintenance, would have kept it since.

As the word *strain* is used in bacterial nomenclature to designate a recognized origin rather than an ensemble of biological properties, its use is suggested when reference is made to the original culture of B.C.G. or to any recognizable type-culture or to any undifferentiated sub-culture. The word *sub-strain* could be used at least temporarily for a culture which is derived from the original culture and is maintained in a given laboratory, but is claimed to be notably modified. The possi-

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bility of agreeing upon a standard culture of B.C.G. to be used as a reference should be investigated.

The first problem consisted in finding out whether the B.C.G. strain had varied in the laboratory of origin or in any of the 50 laboratories of the world which have been using it for varying lengths of time. If there were variations, did they affect the genotype or the phenotype? In the first instance the variants would be stable; in the second instance, the variation could be reversed simply by placing the culture in the original media and conditions of growth and eliminating the carry-over effect.

The Original Description of the Strain of B.C.G.

In order to determine whether or not the B.C.G. strain has changed, we have summarized the *original description* of the type-culture of B.C.G., by Calmette and his co-workers[1] and research workers of the early period. This synthesis covers the period extending from 1919 to Calmette's death in 1933.[1, 2] The original description was confirmed at three international meetings during this period (Paris Conference in 1928,[3] International Congress on Tuberculosis in 1930 and "*Rapports et documents*" published by Calmette in 1932[4]). We believe that it defines the genotype and phenotype formula of B.C.G., *within the limits permissible by the qualitative and the quantitative methods then utilized.*

The properties of B.C.G. have been divided into *positive characteristics* (R stage of the culture, eugonism, facility of maintenance by serial transplantations, toxic and tuberculinogenic properties, *in vivo* vitality or power of producing certain lesions in man and animals, allergenic and immunizing power), and a *negative characteristic*, fundamental and particular to B.C.G., that of hereditary avirulence (according to Calmette's definition of virulence in tuberculosis[1, 2]).

However, these characteristics, taken individually or together, are not sufficient to permit an absolutely specific and positive identification of the strain if its origin and lineage are not known. Investigators should strive to discover still more specific and distinctive characteristics for the identification of the B.C.G. strain.

No definite proof of *qualitative, profound and hereditary* changes in the known properties and potentialities of B.C.G., as described before 1933, can be found in the literature. In this respect, the genotypic and phenotypic formula of B.C.G. seems highly resistant, even to changes of environment. Since 1930, no one has contested the attenuated "virulence" of B.C.G. The use of this term to designate the positive properties of vitality *in vivo* is criticized by several authors who consider that the word "vitality" *in vivo* would be more appropriate and serve to prevent confusion.

Variations in the "in vivo" Vitality of B.C.G.

Several authors fear however that B.C.G. or some of its sub-strains have varied or are still varying in positive characteristics, particularly as regards *in vivo* vitality; in some cases, this vitality may have been lowered under the supposed effect of over-attenuation. After prolonged observation *in man* following the use of B.C.G. vaccine, other authors have reported variations in the activity of a given strain, or of different sub-strains, with regard to allergenic power and production of glandular complications. In the minds of this latter group, who evaluate the strain from the properties of the vaccine, there is no doubt concerning the heterogeneity of B.C.G. (Moreau, French, Danish, Swedish). These variations in its vitality, however, have never risen above the level of pathogenicity for the guinea-pig.

The Particular Sensitivity of Man

Comparison between various strains and sub-strains of B.C.G. in man by means of vaccinal suspensions is subject to hazards and the influence of factors pertaining more to techniques of preparation, preservation and administration of the vaccine than to the distinctive characteristics of a strain. Yet the extensive clinical background of some public health officers or pædiatricians who have reported variations in the effects in man of B.C.G. of various origins deserves close attention. According to Wallgren,[5] man seems to display a sensitivity to B.C.G. different from that of the guinea-pig: he may therefore be considered as a more sensitive reagent for examining the heterogeneity of the sub-strains.

Results of Comparison of Sub-strains using Calmette's Methods

Indeed, the few comparisons of sub-strains based on laboratory tests and animal experiments and made before 1946 with the methods of Calmette and his co-workers,[1] seldom revealed important differences either between sub-strains or in the activity of the same strain thus examined from time to time, except for the facts reported by Jensen.[6] Workers at the Pasteur Institute, who made several such comparisons by the above-mentioned methods between 1928 and 1948, have repeatedly stated that the strain which they use and several other cultures which they have compared with their own do not differ to any great extent.

Maintenance of the B.C.G. Strain in the B.C.G. Laboratories of the World

The survey of the Sub-Committee on B.C.G. of the International Union against Tuberculosis and our own complementary survey of 40 laboratories producing B.C.G. have shown that of 19 laboratories producing B.C.G. from the very beginning, 15 are still using a strain received from the Pasteur Institute; six of these received it during Calmette's life. Four out of six laboratories which

started operating between 1930 and 1938 received their strain from the Pasteur Institute. Of 16 other laboratories which started operations after 1947 (with one exception), seven use a strain received from the Pasteur Institute; the others received their strain from other B.C.G. laboratories.

Only 11 laboratories out of a total of 40 eventually changed their strain because of lack of normal development in culture; 13 others are periodically supplied with lyophilized strain 888 by the Pasteur Institute. As for the maintenance of the strain, 15 laboratories out of 40 use Sauton-potato medium only, three use glycerin-potato only, 16 use both bile-potato and Sauton glycerin-potato media; five use bile-potato; only two laboratories use exclusively passages from Sauton to Sauton. The disparity in the choice of the maintenance media (50% of the laboratories, however, maintain the use of bile) is not as wide as in the alternation of transplants, or series of transplants on different media. The periodicity of transplantation is practically the same everywhere for a given medium. The process adopted by each laboratory is empirical and adheres faithfully to a given technique.

In summary, the difficulties encountered by a few laboratories in the growth and culture of the strain are not necessarily due to variation phenomena of major biological interest, but to the local production technique. The experimental and routine observations made under the conditions prevailing in most production laboratories have not apparently revealed any obvious variations in the strain.

The Dissociation of B.C.G.

Even before 1933, B.C.G. had been dissociated experimentally into R and S colonies by several authors. The claims of a few authors concerning the virulence of the S dissociant were not maintained after 1930, in spite of improved methods of testing. Recently discovered facts about the dissociation of B.C.G. suggest morphological and physiological analogies with these earlier claims. The S variety obtained by Saenz and Costil[7] and by Birkhaug,[8] and the "spreading" variety obtained by Pierce and Dubos,[9] for example, seem more highly immunogenic and possess a greater vitality *in vivo* than the other variants of the same cultures.

Certain authors were impressed with the idea that the dissociation phenomena could supply information about the stability or the heterogeneity of B.C.G.; no wonder, then, that studies on dissociation are often linked with those concerning the stability of B.C.G. This hypothesis has recently received an interesting confirmation through the quantitative work of Dubos and his associates,[9, 24, 25] who demonstrated that certain activities of some B.C.G. sub-strains correlate with their content of the three morphological dissociants. However, according to these authors, the *in vivo* vitality of morphologically identical dissociants of the various sub-strains studied is related to the particular vitality of each original sub-strain. The dissociants do not possess by themselves a greater differential activity *in vivo* than that of the whole sub-strain.

More Recent Comparisons of B.C.G. Strains

More recent (1946-57) comparisons of a given strain or sub-strain, made either periodically or at intervals of several years, or of several sub-strains at one time, *using the conventional methods for the study of B.C.G.* in vitro *and* in vivo, are stated by the authors to have shown no notable difference in the stability of B.C.G. The exception—Boe's findings in guinea-pigs—is to be taken up later. Most of these workers, as well as those who studied the subject before 1946, agree that the B.C.G. strain is remarkably stable in respect to the properties referred to in the original description, where the guinea-pig was the mainstay of the experimental work *in vivo*. Regardless of the number of passages on bile potato,[10, 11] or of the origin of the strain or of occasional switches of strain,[12-15] or of the origin and the maintenance technique of the sub-strain,[16-18] the antigenicity, the allergenic and immunizing power in the guinea-pig mainly remains unaltered. According to Fenner,[19] the variety of culture media used by the above authors to study the immunogenic power and the "virulence" of B.C.G., as well as the constancy of results obtained, is proof of the stability of properties of B.C.G. If this apparent stability of all known characteristics of B.C.G., particularly as observed in guinea-pig experiments, should prove real, the genotype of the strain or of the sub-strains would not differ from that of the original strain or type-culture. The minor occasional changes, observed *in vitro* or *in vivo*, would correspond to phenotype variations and would therefore be reversible if the cultures were returned to and kept in the original media.

New Facts about the Heterogeneity of the B.C.G. Strain

Several facts reported since 1946 weaken the claim of the supporters of the stability of B.C.G., as described above. The problem of stability or heterogeneity of B.C.G. rests on two important properties, i.e. so-called "virulence" or *in vivo* vitality of B.C.G., and post-vaccinal glandular involvement. According to most workers, guinea-pig reactions do not bring out differences between sub-strains of B.C.G. in these respects. Nevertheless, observations made in man by experienced clinicians and those made by contemporary research workers give serious cause for questioning the stability of the B.C.G. strain. As already mentioned, these observers maintain that the human body is a more sensitive reagent than the guinea-pig for distinguishing differences between sub-strains, the vitality of which however always remains below the level pathogenic for the guinea-pig. The following sub-strains have been studied extensively and attempts have recently been made

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to establish their characteristics: a so-called Moreau sub-strain, a Danish sub-strain, a Swedish sub-strain and a French sub-strain. These clinical observations[5, 16, 20-23] fall in line with other data supplied by the research workers[6, 23-25] who have demonstrated the heterogeneity of certain sub-strains of B.C.G. by the use of qualitative and quantitative methods different from those which led to the original description of the B.C.G. strain.

Some authors ascribe these variations to the influence of the culture medium and to the alternation of transplants (particularly bile or Sauton's medium), but the work of van Deinse and Sénéchal,[26] and others, shows that the use of bile does not alter the culture so much as repeated passages on Sauton's medium and that even without bile a culture maintained constantly on Sauton's liquid medium recovers its vitality on potato.

The following facts concerning the Moreau sub-strain are disturbing. Patients receiving large doses of this sub-strain by mouth fail to show any glandular involvement. It shows a reduction of the other expected characteristics when studied *in vivo*[27] and it lacks the spreading variant and the cord factor formation when studied *in vitro*.[9] However, Gernez-Rieux[28] and Fourestier and his co-workers[29] have administered orally the vaccine of the Pasteur Institute without giving rise to any more glandular involvement in man than had been observed with the vaccine made up with the Moreau sub-strain in the hands of the Brazilian authors, although both groups used identical dosages.

The sub-strain which Rosenthal[30] abandoned because it did not immunize the mouse as well as formerly and formed less cord factor, may also be mentioned at this time.

In Boe's[16] opinion, a vaccine prepared from a French strain gave rise to more frequent abscesses and adenitis in man than did a vaccine prepared from a Norwegian strain. This did not apply to the guinea-pig. This French strain sensitized man and guinea-pig more intensely than did Danish and Swedish strains which occupied an intermediate position in this respect. One cannot ignore van Deinse's[31] reports on the extraordinary behaviour in Holland and in Poland of a strain from Copenhagen, which gave rise to an unusual frequency of glandular involvement in subjects immunized by mouth. The Swedish sub-strain, always maintained on bile-potato medium, seldom gives rise to such a response. Some authors claim that its mild action is probably due to the fact that in its preparation the vaccinal suspension is allowed to settle before being standardized. The Danish sub-strain is maintained only by Sauton passage, the Moreau sub-strain by Sauton-potato or glycerin-potato alternating with bile-potato, the French sub-strain on Sauton-potato medium including three successive yearly passages on bile-potato medium.

Heterogeneity in Man and Mice, Homogeneity in Guinea-pigs?

It remains to be determined whether or not the heterogeneity of B.C.G. sub-strains, as disclosed experimentally *in vitro* and in the mouse but seldom in the guinea-pig, corresponds to an identical heterogeneity in man. Does this heterogeneity reflect phenotypic or genotypic differences? It is reasonable to suppose that the large doses of B.C.G. usually employed in the guinea-pig to test the irritating, immunizing and sensitizing power of the vaccine saturate the animal, thereby preventing the appearance of differences which could be appreciated in a more sensitive animal such as man or by other means altogether. This would invalidate the research purporting to reveal changes in the original strain of B.C.G. by comparison with the original description. If this strain has varied within limits not definable by earlier conventional experimental methods, reference to the original description in relation to newer, more sensitive and quantitative techniques would be meaningless. The problem of the stability of B.C.G. has a theoretical and practical bearing. Its study has already opened new avenues of thought. It would be interesting to assemble in a single laboratory the largest possible number of B.C.G. sub-strains and to maintain them long enough on the same original culture medium (bile-potato or glycerin-potato) to remove the effects of the carry-over and reproduce, if possible, the conditions which favoured the development of the original phenotype. Then they could be compared among themselves in all respects, by the conventional and the more recent experimental methods *in vitro* and *in vivo*, and, in man, by using vaccine preparations produced and standardized under identical conditions with the help of the latest control techniques.

II. CONTROL OF THE B.C.G. STRAIN

Up to at least 1948 it is presumed that no other control than that recommended by the Pasteur Institute (on the vaccine suspension) was suggested and practised. This control was limited to safety testing. In 1956, the survey of the Sub-Committee on B.C.G. showed not only that uniformity of direct control of the strain was far from having been reached, but also that several laboratories were completely or partly dispensing with it, while others were limiting themselves to a few tests. Control of the vaccine generally serves as control of the strain.

Although it is not routinely done, we feel it advisable to exercise direct control of the B.C.G. strain, first upon receipt and periodically thereafter. Control of the strain or of a sub-strain *by means of the vaccine* becomes over-burdened with extrinsic factors inherent in the vaccine and in the human element, and often quite unrelated to the strain itself.

Evaluation of a Method of Control

A quantitative method of control would call for determination of the statistical variation of its results, its margins of error and, if sufficiently standardized, the expected variations from one laboratory to another. Such methods could eventually provide a genuine international control of the stability of B.C.G. Joint research, similar to that initiated by the International Children's Centre in various laboratories, cannot help but stimulate and enrich such techniques.

Devising a Method of Control

Control of a strain used for vaccine preparation should cover the identity of the strain, its antigenic power and its activity in animals, and finally, as a corollary, the stability of its properties while in continuous use.

B.C.G. specialists must exercise their ingenuity in perfecting reliable experimental methods for the control of the strain used for making the vaccine and thus avoid, if possible, the practice of controlling the strain in man.

There are several aspects and problems related to control of the B.C.G. strain: qualitative determination of the variety *Mycobacterium tuberculosis* var. *bovis B.C.G.*, quantitative determination of the characteristics particular to a strain or sub-strain of B.C.G., control of the strain or of the sub-strain upon receipt, periodical control, sensitivity and uniformity of methods and variability of results, absence of a standard strain (if we except the periodical shipments of the lyophilized strain 888 from the Pasteur Institute to B.C.G. laboratories), and finally distribution of the various stages of control between production laboratories on the one hand and certain regional control laboratories on the other hand—the latter being more specifically charged with the quantitative control of the particular characteristics of the B.C.G. strain or sub-strain used for production. Production laboratories would then exert only specific control of the B.C.G. strain; that is, determination of the variety *bovis B.C.G.*

Were it firmly established that lyophilization of B.C.G. entails no selection of variants, distribution of lyophilized and internationally recognized strain or sub-strain would settle the second or more difficult type of control, i.e. *determination of the particular characteristics of the B.C.G. strain* or of a sub-strain and of their stability.

Usable or Promising Techniques

We have enumerated and described 29 different techniques, qualitative or quantitative, usable or promising, which could serve in attempting the control of the B.C.G. strain. The first 16 could be used for specific identification of the strain; however, none of them taken singly or associated with other techniques gives enough information to identify with certainty the strain or a sub-strain as being B.C.G., unless the origin and lineage of the culture is known. This control is more or less presumptive, but it must be made on a known strain with as much stringency as if the strain were unknown. The other quantitative tests which permit determination of properties of the strain or of a sub-strain of B.C.G., complete and evidently reinforce specific and qualitative control. This quantitative control becomes all the more imperative because a certain degree of heterogeneity in the B.C.G. strain is conceded by several authors. However, it would be useless to overburden the producers with technical obligations not based upon thorough experimental studies.

Selection and perfection of thoroughly tested quantitative techniques are therefore urgently needed. These should afford a rapid experimental control, both *in vitro* and *in vivo*, of the essential characteristics of the strain or of the sub-strains of B.C.G. to be used in vaccine manufacture.

If the different sub-strains are really heterogeneous and have certain specific effects on humans, production laboratories might take advantage of such characteristics and apply them according to the needs of the local population. This seems to have happened spontaneously already.

SUMMARY

The authors summarize the general biological study of the B.C.G. strain which they presented at the International Technical Conference on B.C.G. in Geneva, in 1956.

They discuss the pros and cons of the homogeneity or heterogeneity of the B.C.G. strain.

It seems: (1) that man is a more sensitive index to B.C.G. vitality than are other animals; (2) that some well-controlled observations in man and newer experimental methods have disclosed a certain heterogeneity of the B.C.G. strain which had not and could not have been shown with the conventional methods employed in the days of Calmette.

The authors also propose a system of control and describe several methods that could be used not only to ascertain the safety, identity and antigenicity of a B.C.G. strain or sub-strain, but also to attempt determination of its particular characteristics.

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RÉSUMÉ

La Conférence Internationale Technique du BCG s'est réunie à Genève du 2 au 6 octobre 1956, sous les auspices de l'Union Internationale contre la Tuberculose. Son but était d'amorcer des discussions, entre experts de la préparation et de l'emploi du vaccin BCG dans les divers pays du monde, sur la souche du BCG, la préparation du vaccin, son contrôle et sa conservation par lyophilisation. La Conférence avait été bien préparée par l'envoi d'un questionnaire concernant le détail de ces divers problèmes aux 48 laboratoires qui produisent et étudient le vaccin.

Les auteurs ont préparé le rapport sur "La Souche du BCG", sujet qui a donné lieu à des études importantes depuis quelques années. Calmette considérait sa culture comme une souche d'*atténuation fixée* et voilà plus de vingt-cinq ans que cette atténuation de la virulence est admise de façon très générale, tant par les expérimentateurs que par les cliniciens. Le problème de la variation du BCG revient à l'ordre du jour depuis une dizaine d'années mais il est soulevé par les différences qui ont été constatées dans l'intensité de l'allergie et des réactions ganglionnaires lorsque l'on emploie des vaccins de diverses origines. Ces différences ont été attribuées à la méthode de vaccination et à l'état des sujets vaccinés, à la préparation du vaccin, mais aussi aux propriétés des cultures entretenues dans les divers laboratoires à partir de la souche originale du BCG.

En vue d'établir les variations possibles de certaines cultures du BCG, les auteurs reconstituent, d'abord, d'après les travaux de Calmette, de ses collaborateurs et de ses contemporains, la description-princeps des propriétés du BCG, puis ils montrent que les variations de cette souche doivent être recherchées en tenant compte des données de la génétique. Il sera, ainsi, possible de savoir si ces variations intéressent le génotype du BCG ou, simplement, son phénotype. Les rapporteurs proposent de réserver le nom de souche à la culture originale du BCG ou à toute culture-type qui serait agréée par un accord international et d'employer, au moins de façon temporaire, le mot "sous-souche" pour une culture dérivée de la culture originale et qui après avoir été entretenue dans un laboratoire paraît notablement modifiée.

Les auteurs montrent que la souche du BCG n'a pas varié dans ses propriétés négatives et en particulier dans son avirulence héréditaire (au sens admis par Calmette), mais que ses caractères positifs (bactériologiques tuberculinogène, allergène, immunogène, vitalité *in vivo* ou pouvoir de produire certaines lésions chez l'homme et l'animal) semblent montrer certaines variations dans des cultures telles que les souches française, danoise, Moreau, suédoise. Il est bien entendu que la vitalité du BCG ne s'élève, en aucun cas, au-dessus du niveau de la pathogénicité pour le cobaye.

A la faveur d'une enquête personnelle à laquelle ont répondu 41 laboratoires, les rapporteurs ont constaté la variété des méthodes utilisées pour entretenir le BCG, mais aussi la remarquable stabilité des propriétés culturelles et des effets du BCG chez le cobaye. Ses résultats n'infirment pas cependant ceux des chercheurs qui, avant 1933, ont dissocié le BCG en colonies R et S, ni ceux de Dubos et de son école qui montrent l'hétérogénéité de diverses sous-souches du BCG, les propriétés caractéristiques des dissociants morphologiques, en utilisant comme critères des épreuves nouvelles et, en particulier, l'inoculation à la souris. Cette hétérogénéité est confirmée par les observations cliniques rapportées à la Conférence de Varsovie en 1954. Il semble que le cobaye, généralement employé pour étudier le BCG, ne révèle pas des différences auxquelles sont sensibles l'homme et la souris.

Les auteurs proposent un ensemble de recherches pour élucider cet important problème de l'homogénéité ou de l'hétérogénéité de la souche du BCG et, en particulier, pour étudier l'influence des conditions de culture.

Ils proposent également un ensemble de règles et de méthodes (29) pour assurer le contrôle qualitatif et quantitatif de la souche du BCG. Ce contrôle pourrait être réparti entre divers laboratoires internationaux, régionaux et locaux qui assumeraient ces diverses étapes.

THE DIAGNOSTIC IMPORTANCE OF THE MYXŒDEMA REFLEX (WOLTMAN'S SIGN)

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IN PATIENTS WITH myxœdema,* the muscle stretch reflexes usually show a characteristically delayed relaxation after contraction. I wish to report my experience with this helpful diagnostic sign, the "Woltman sign of myxœdema" or "myxœdema reflex", which surely deserves far more attention than it has heretofore received. It is "probably more specific for the diagnosis of myxœdema than the basal metabolic rate."[1] "This sign is invaluable as a clinical test for confirming the diagnosis of suspected myxœdema; or, as often happens in practice, the recognition of slow relaxation of reflexes may initiate the suspicion of myxœdema in the first place."[2]

This is one reason why several reflexes should be checked as part of every physical examination. When one considers how often the diagnosis of myxœdema is missed, and conversely how many euthyroid patients are mistakenly treated with thyroid extract, it is apparent that anything that assists in the diagnosis of myxœdema is of great value.

My interest in the myxœdema reflex was aroused during a year of postgraduate study at the University Hospital, Saskatoon, in 1955-56. This im-

*The term "myxœdema" is used to denote a clinically significant degree of adult hypothyroidism, although the purists may consider that the term should be applied only to the patient's appearance and not to the diagnosis.

portant sign was unknown to any member of the rather cosmopolitan house staff (40 interns from 23 universities in 15 countries), until it was called to our attention by the neurologist. It was well demonstrated in several cases of myxœdema and later led me to the correct diagnosis and treatment of a patient with myxœdema who had been given a diagnosis of "hypoplastic anæmia" on three previous admissions.

Its value has been substantiated since my return to general practice, as I have seen five new cases of myxœdema in five months. All had a positive myxœdema reflex and the diagnosis was confirmed by clinical and laboratory findings. Previous examinations had not established the correct diagnosis in four of these patients. The fifth case would certainly have been missed, had my attention not been aroused by the finding of a positive myxœdema reflex at the conclusion of the examination.

History.—Chaney[3] first described tendon reflex changes in myxœdema in 1924, with detailed studies of reflex duration in four patients. He stated that ". . . myxœdema is apparently the only condition in which the tendon reflexes are much slower than normal . . ." ". . . [this] should be a helpful sign because of its simplicity, its clear-cut nature and its limitation to this one disease."

In 1951, Lambert and his colleagues[1] reported on 115 patients with myxœdema and 121 with other conditions in which the ankle jerk was graphically recorded with special apparatus. Of the patients with myxœdema 77% had a mean duration of ankle jerk longer than 0.46 second. Normal persons and patients with other conditions had a mean duration of ankle jerk less than 0.46 second. In all the 55 patients with myxœdema studied during treatment with thyroid the duration of ankle jerk decreased.

Between 1924 and 1951, only six reports (a total of nine cases)[4-9] of this reflex in myxœdema appeared in the literature. Three of these reports were from the United States, two from Sweden and one from Uruguay. It has since been mentioned during a recent clinico-pathological exercise at the Massachusetts General Hospital.[10]

The reflex is mentioned in the new Mayo Clinic text *Clinical Examinations in Neurology*[2] and is there referred to as "Woltman's sign of myxœdema". Although usage of eponyms is frowned upon, it may be appropriate to recognize in this manner the eminent neurologist who first used this sign almost 40 years ago.

Few textbooks of neurology, endocrinology or medicine mention this sign, or if it is mentioned, it is not adequately stressed. Two exceptions are the statements by Rawson and Rall in Duncan's *Diseases of Metabolism*,[11] "The reflexes are characteristic with a normal rate of contraction and a very prolonged rate of relaxation", and by Thorn, Forsham and Hill in Harrison's *Principles of Internal Medicine*:[12] "The relaxation of the deep tendon reflexes may be characteristically slowed in patients with myxœdema." Parker stressed the importance of this reflex in his *Clinical Studies in Neurology*.[13]

METHOD OF ELICITING WOLTMAN'S SIGN

The tendo achillis is the best site at which to demonstrate this sign, but it is sometimes detected at the biceps or in other muscle stretch reflexes. Once a doctor has seen the diagnostic slow relaxation in a typical case of myxœdema, his attention will be drawn to it on routine examination in unsuspected cases.

The patient is seated on the examining table, with lower legs dependent, so that the relaxation phase of the ankle reflex will be in an opposite direction to gravity and thus more readily apparent. The foot is held gently in one hand and the tendo achilles tapped with a reflex hammer with the other hand. The magnitude of deflection may be somewhat diminished or may be normal, and the speed of contraction is comparable to any normal reflex response. The crucial part is the relaxation phase; instead of quickly returning to the starting position, the foot comes back very slowly, taking almost a full second to return. Although this is a subjective observation, once one has felt the slow relaxation of a myxœdema reflex it is surprisingly easy to differentiate this from a normal reflex.

This sign, when present, is virtually diagnostic, as there are no "false positives" recorded in the literature. Of course, some patients with myxœdema will have reflexes that are absent or so weak that the slow relaxation is not apparent.

CASE REPORTS

CASE 1.—Mr. W.M., a 63-year-old farmer, was admitted on June 22, 1956, with complaints of cough, shortness of breath and hoarseness for one week, and trouble in swallowing and wheezing for one day. Initial investigation was directed to these symptoms, and only later did questioning reveal that for several years he had noted weakness, easy fatigability, lack of energy, sensitivity to cold, slight deafness and hissing noises in his ears. He had lost 10 lb. in weight. Family and past history were noncontributory.

The following details were not all noted during the initial examination. His height was 5 ft. 8 in. and he weighed 120 lb. He had a rather expressionless face, his thinking was slow and his speech hoarse and hesitating. The skin showed a rather waxy pallor and was slightly dry. The outer thirds of the eyebrows were sparse and the eyebrow hair was coarse; otherwise the hair was fine but dry. He had complete dentures. The right lobe of the thyroid was just palpable. Laryngoscopy revealed the vocal cords to be œdematous and slightly inflamed. There was one palpable left axillary node. The lungs were clear. The heart was clinically not enlarged and there were no murmurs. Blood pressure was 134/80 mm. Hg. The pulse was 68 and regular. The dorsalis pedis and posterior tibial pulsations were not palpable on the right and were barely palpable on the left. Vibration sense was absent in the toes. The tendon reflexes were sluggish. The ankle reflexes particularly showed a normally quick contraction and a very slow relaxation.

He was given increasing doses of thyroid once the diagnosis was established. When discharged on July

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30, he was taking 60 mg. thyroid daily. He is again able to do full farm work.

CASE 2.—Mrs A.H., a 39-year-old farm housewife, was admitted on July 29, 1956, with complaints of being weak and tired, having no ambition and continually feeling cold for six months. On questioning, she stated she was more lethargic in movement and speech and her friends had remarked that her voice was becoming deeper. She had taken iron for her mild anæmia for several months without improvement.

The skin was pale and dry, the hair dry and somewhat coarse, and the outer thirds of the eyebrows rather sparse. The thyroid was not palpable. The lungs were clear and the heart was normal. B. P. was 110/75 mm. Hg. The pulse was 64, regular but somewhat weak. The knee and ankle jerks showed a normal contraction and a very slow relaxation. She was 5 ft. 2 in. in height and weighed 128 lb.

pulse 68. The extremities were cold. Tendon reflexes were somewhat sluggish, with normal contraction and a slow relaxation of the ankle jerks.

She was discharged taking thyroid 90 mg. daily. On September 7, she reported more energy, greater tolerance to cold, better appetite and a greater sense of well-being. Her tendon reflexes had returned to normal.

CASE 4.—Mrs. L.A., a 24-year-old housewife, was seen on October 25, 1956, complaining of lack of energy. She volunteered that she had been stumbling for two weeks, and had noticed puffiness of the hands for a similar period. She had gained 10 lb. in the past two years. During five years of marriage, both pregnancies had ended in miscarriage; one at three months in February 1956 and one at two months in April 1956. Further questioning revealed that low temperatures had bothered her all her life and she

TABLE I.—LABORATORY INVESTIGATIONS

	1. *Mr. W.M.*	*2.* *Mrs. A.H.*	*3.* *Mrs. A.S.*	*4.* *Mrs. L.A.*	*5.* *Mr. C.J.*
Basal metabolic rate	−26	−16	−20	−25	−28
Serum cholesterol (mg. %)	hæmolyzed	342	250	445	345
Protein bound plasma iodine (micrograms %)	hæmolyzed	4.3	—	less than 1.0	4.0
Hæmoglobin (15.6 g.% = 100%)	97%	73%	81%	71%	102%
Red blood cells (million per c.mm.)	4.70	3.80	4.01	3.41	—
White blood cells (per c.mm.)	5400	5700	6000	6450	8150
Differential count	normal	normal	normal	normal	normal
Sedimentation rate (Westergren in one hour)	6 mm.	61 mm.	—	37 mm.	6 mm.
Urinalysis	neg.	neg.	neg.	neg.	neg.
Heart size (chest radiograph)	normal	normal	—	slightly enlarged globular	slightly enlarged

When discharged, she was taking thyroid 60 mg. daily, and Ferrobex* one tablet three times a day. On September 27, her Hb. value was 78%, B.P. 118/75 mm. Hg and she was looking and feeling much better. At this time, the tendon reflexes reacted normally, both on contraction and relaxation. She is now well on thyroid 90 mg. daily.

CASE 3.—Mrs. A.S., a 52-year-old farm housewife, was admitted on August 17, 1956, complaining of constipation, anorexia, weakness, tiredness and frequent head colds. She felt cold and even in summer was rarely comfortable. These symptoms had been present as long as she could remember. Her periods had been irregular for two years, with menorrhagia a year before and five months' amenorrhœa during the winter. She had had a tonsillectomy at age 21 and a cervical polyp had been removed at age 51. A month previously she had been diagnosed as having neurasthenia and psychoneurosis.

She was a listless, slow-moving, slow-thinking woman with a monotonous, flat and somewhat low-pitched voice. She was 5 ft. 4 in. in height and weighed 115 lb. The skin was pale and dry and the outer thirds of the eyebrows were somewhat sparse. The hair was fine but dry. The thyroid was not palpable. The lungs were clear and the heart was not clinically enlarged. B.P. was 124/80 mm. Hg and pulse 72 and regular. Two days later, B.P. was 104/54 and was "always freezing". She had noticed her voice to be husky and deeper for six months and there had been some slowing in her thinking and movements.

Fig. 1.—Case 3.

Her face was puffy, particularly in the eyelids and below the eyes. The eyebrows were wiry but the hair was otherwise fine. The skin was pale, puffy and dry (Fig. 2). Her height was 5 ft. 4 in. and her weight 150 lb. There was some supraclavicular fullness. The thyroid was not palpable. The heart and lungs were normal.

*Ferrobex has the composition:
Ferrous gluconate 5 grains (300 mg.)
Copper 0.006 grain (0.4 mg.)
Thiamine chloride 0.5 mg.
Riboflavine 0.5 mg.
Nicotinamide 2.0 mg.

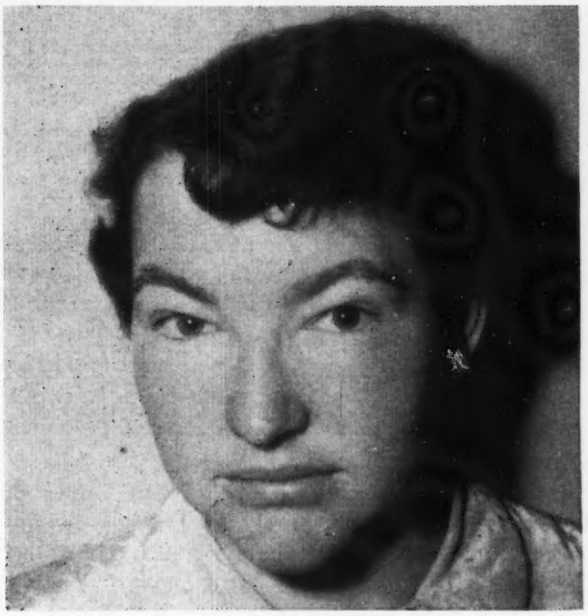

Fig. 2.—Case 4, before treatment.

Fig. 3.—Case 4, after treatment.

B.P. was 118/80 mm. Hg, and the pulse 64, weak but regular. There was little hair on the limbs but she stated that this had always been the case. The ankles were thickened by non-pitting œdema. Tendon reflexes were present and equal, with a normal contraction but very slow relaxation, best noted in the Achilles reflex.

On November 27, her weight was 5 lb. less, her voice higher and less husky, and her rings were loose. She no longer stumbled. She had had a heavy menstrual period of two weeks' duration and her hæmoglobin value was down to 44%. Ferrous gluconate 300 mg. three times a day was added to her therapy.

On January 15, 1957 (Fig. 3), all puffiness of her face and hands was gone and her ankles were much slimmer. She had had her rings made smaller. She was comfortably warm, had a lot more energy and was thinking and moving faster. Her voice was more feminine. Hb. value was now 77%. She is well on a maintenance dose of thyroid 90 mg. daily.

CASE 5.—Mr. C.J., a 72-year-old retired farmer, was seen on November 6, 1956, complaining of being lazy, sleepy and not feeling well. "I'm just not a hundred per cent." He had gained in weight, from 175 to 191 lb., and was constipated. Towards the end of his examination, the myxœdema reflex was elicited; only then did more specific questioning disclose that his speech had gradually slowed down during the past year, his voice had been deeper for one month, and he had been a little hoarse for several weeks. He said he felt "wobbly". He required ten hours' sleep each night, and would fall asleep sitting up during the day. Past illnesses included an appendectomy in 1929, a *thyroidectomy* in 1944, and a prostatectomy in 1952 and a cataract operation in 1954.

Examination revealed a previous iridectomy on the right. Fundi showed arteriolar sclerosis and slight arteriovenous nicking. His height was 5 ft. 9 in. and he weighed 191 lb. His hair was dry but fine (Fig. 4). There were complete dentures. An old transverse thyroidectomy scar was present and a firm nodule was palpable in the right lower lobe of the thyroid. The chest was sthenic with an increased antero-posterior diameter, a thoracic index of 24/30, and only one inch of diaphragmatic excursion. A few moist rales were heard at both bases. The heart was not clinically enlarged. B.P. was 104/40 mm. Hg. Pulse was 58 and regular. There was an old appendectomy scar and an old suprapubic scar with incisional hernia. Small external hæmorrhoids were present and the prostatic bed was very hard. Reflexes were sluggish; the right ankle jerk was unobtainable and the left ankle jerk showed a diminished though normally quick contraction, but relaxation was markedly slowed.

He was given thyroid 15 mg. daily, gradually increased to 60 mg. On February 1, 1957, his weight was 189 lb. with B.P. 104/70 and pulse 68. He felt "peppier", was not so lazy or sleepy, moved and talked faster, could walk better and was no longer "wobbly".

DISCUSSION

The finding of five new patients with myxœdema in five months in a general practice suggests that

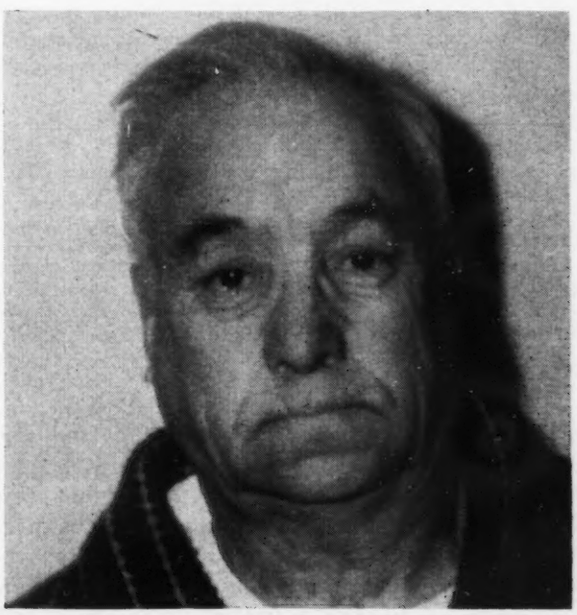

Fig. 4.—Case 5.

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this condition may be more common than generally appreciated. It should be noted that the patients' presenting complaints are usually commonplace and non-specific. The physical signs are easily overlooked unless the doctor is alert to their significance. Only when the diagnosis has once been entertained does careful questioning elicit the usual symptoms of myxœdema.

Four of these patients developed "spontaneous" myxœdema, without any history of ingestion of iodide, thiocyanate or para-aminosalicylate. One developed signs and symptoms of myxœdema 12 years after thyroidectomy.

All five patients showed lassitude, intolerance to cold, change in voice, slowness of thought and movement, pale dry skin and change in facial configuration. The eyebrow hair was coarse and wiry in two cases; otherwise the hair was described as fine, though dry, in four cases, and as coarse in only one case. Two patients complained of constipation, two of stumbling gait, and two of gain in weight. The blood pressure in all five was relatively low and the pulse slow, tending to be weak.

Radioactive iodine studies were not available. Protein-bound iodine estimations were low enough to be diagnostic in only one of three cases. The serum cholesterol was elevated in all four cases where this test was completed. The basal metabolic rate was low in all five cases.

The Woltman sign of myxœdema was present in all cases.

A plea is made for greater awareness of myxœdema in all patients complaining of any of the chief symptoms mentioned above. Probably in few other diseases is the diagnosis so often missed. The Woltman sign of myxœdema, once learned, is a useful diagnostic aid and in many instances will by itself suggest the correct diagnosis. This is all the more important because myxœdema is such a satisfactory disease to treat.

SUMMARY

In five consecutive cases of myxœdema occurring in a general practice the classical Woltman sign of myxœdema was present. This was of great value in confirming the diagnosis or even first suggesting the diagnosis. The usefulness and reliability of this sign is stressed.

I would like to express my appreciation to my colleagues, Dr. C. J. Houston and Dr. H. Crossley, who allowed me to report on Cases 3 and 2 respectively, after they had noted the presence of the myxœdema reflex. I am indebted to Dr. A. A. Bailey, neurologist at the University Hospital, Saskatoon, for his encouragement and helpful suggestions.

ADDENDUM

Three more patients with myxœdema have been seen in the five months since the preparation of this paper was begun. All had the myxœdema reflex. One patient had been undergoing hospital investigation for anæmia and weakness for two weeks when, during a complete recheck examination, I was surprised to note a typical myxœdema reflex.

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RÉSUMÉ

Le diagnostic de myxœdème n'est pas toujours facile à poser. À moins qu'il ne crève les yeux, la plupart des praticiens ont tendance à l'omettre de leur diagnostic différentiel. Le signe décrit par Woltman il y a environ 40 ans revêt donc une importance considérable tant par la simplicité de son interprétation que par sa précision. C'est un fait reconnu chez les myxœdémateux que les muscles striés se relâchent beaucoup plus lentement après une contraction que les muscles des personnes normales. Ce retard dans la décontraction se manifeste dans un grand nombre de réflexes communément recherchés au cours de l'examen neurologique. L'auteur, qui s'en est servi à maintes reprises, prétend que le tendon d'Achille est l'endroit le plus favorable à sa manifestation. Le signe disparait lorsque l'équilibre thyroïdien est rétabli et que les réflexes redeviennent normaux. Cinq cas tirés des dossiers de l'auteur sont présentés en exemple.

EFFECTS OF SEROTONIN ANTAGONISTS IN NORMAL SUBJECTS AND PATIENTS WITH CARCINOID TUMOURS

Intravenously administered serotonin in man in sufficient dosage caused flushing and reproduced other clinical manifestations of the carcinoid syndrome. Lowering of the arterial pressure in one patient invariably provoked attacks of flushing, suggesting that hypotension directly or through vasomotor reflexes may stimulate the tumour to liberate excessive amounts of serotonin.

1-Benzyl-2,5-dimethylserotonin (BAS) and 2-bromo-d-lysergic acid diethylamide (bromo-LSD), though potent serotonin antagonists *in vitro*, were ineffective orally in controlling symptoms in carcinoid patients. Chlorpromazine appeared to be partially effective in alleviating the symptoms of the carcinoid syndrome.

Bromo-LSD, intravenously administered, did not effectively block, although it may have diminished, the vascular and other pharmacologic effects of intravenously injected serotonin. Bromo-LSD did not cause hallucinations, but in large intravenous doses produced psychic disturbances that otherwise resemble those regularly observed after small doses of lysergic acid diethylamide. These psychic effects of bromo-LSD might be due to inhibition of some central nervous action of serotonin but they were not prevented by the hyperserotonæmia present in carcinoid patients and were not alleviated by infusions of serotonin in normal subjects, as was to be expected by the failure of serotonin to pass the blood-brain barrier.—R. Schneckloth *et al.*: *Circulation*, 16: 523, 1957.

A NATURAL WARM "AUTO-ANTIBODY"

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With the technical assistance of
JULIETTE SIMARD, R.N., R.T.

IN RECENT YEARS, a great deal of time and attention have been given to the study of auto-immune hæmolytic disease. The content of anti-red cell antibodies in normal serum has also been investigated. Rosenthal[1] has described the reversible agglutination of trypsinized red cells by normal serum. Spaet and Kinsell[2] have dealt with the same problem. In 1950, Dacie[3] described the presence of a cold auto-antibody of the incomplete type in normal serum. The complete type of cold antibodies has been known for a long time. The fact that normal serum is so rich in anti-erythrocyte properties cannot but impress those who attempt to explain the pathogenesis of auto-immune hæmolytic diseases; it is quite tempting to establish a relationship between findings in the normal state and what happens pathologically. We have thought that it would be both interesting and worthwhile to search for the presence of an auto-antibody in normal serum at 37° C., this being the temperature of physiological reactions. In the demonstration of this antibody, we have tried to avoid any artificial modifications of the red cells, modifications which—at least theoretically—would seemingly deviate from the natural process. Our work has been profitable; there exists an auto-antibody in normal serum, it is active at 37° C., and it is detectable in most normal subjects and easily demonstrated.

The present paper, which describes some of the characteristics of this antibody, constitutes only a preliminary report of our work.

I. THE WARM AUTO-ANTIBODY IN NORMAL SERUM

GENERAL METHODS

Antiglobulin serum.—Antiglobulin serum was prepared according to Slavin's technique.[4] Our rabbit antisera possess a strong antiglobulin action and are capable of agglutinating human red cells sensitized with an incomplete anti-D, up to a dilution of 1:4096 of the antiglobulin. Needless to say, species agglutinins had been previously absorbed. We have also tried commercial antiglobulin sera (Coombs' sera, made by Ortho and by Knickerbocker).

Antimacroglobulin serum.—The serum of a patient (Mr. H.) suffering from macroglobulinæmia was used as a source of macroglobulin. The immunization process was the same as in preparation of ordinary antiglobulin, except in the preparation of macroglobulin injected into rabbits. Macroglobulin was precipitated from the patient's serum by distilled water, the precipitate was then washed eight times in 250 times its volume of distilled water and thereafter resuspended in a barbital buffer and its electrophoretic migration studied (Fig. 1).

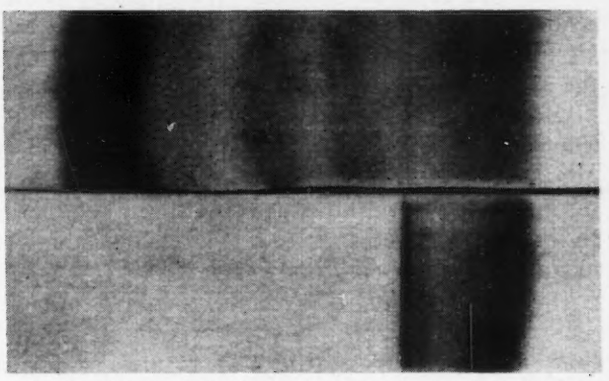

Fig. 1.—Upper part: Normal, paper electrophoresis. Lower part: Electrophoretic migration of the purified macroglobulin precipitate.

Paper electrophoresis.—For electrophoresis, we utilized a bath made in England (EEL), and a Heathkit (USA) transformer. Whatman 3MM paper bands were arranged horizontally. Fractionation operated at 250 volts during five hours, or 125 volts during ten hours.

Collection of blood.—Blood was collected in syringes prewarmed at 37° C., and poured into tubes kept at the same temperature. These tubes were immediately placed in a water bath at 37° C. Serum was separated after centrifugation at 37° C. The red cells were washed at least twice with warm saline. Then both serum and red cells were put in contact in the proportions and according to the methods we describe below.

Coombs' reaction.—The reaction was performed in the tube according to the classical technique. Before Coombs' antiglobulin serum was added, the sensitized cells were washed at least four times. Other methods will be described as the work proceeds.

II. RESULTS

Our work demonstrates that, with sufficient incubation, an "auto-antibody" active at 37° C. can be found in most normal human sera through Coombs' antiglobulin reaction. We shall describe some of the properties of this substance.

1. *Proportions of serum and red cells.*—The most suitable proportions are: 0.1 c.c. of a 2% red cell suspension with 0.3 ml. of serum from the same person. Positive Coombs' tests may be obtained with different proportions, but the reaction is usually less intense.

2. *Incubation time.*—Table I demonstrates that a rather long incubation of the serum-red cell mixture is necessary. In most cases, a two-hour incubation appears sufficient; yet the reaction is always stronger after a five-hour incubation.

TABLE I.—INTENSITY OF COOMBS' REACTION ACCORDING TO INCUBATION TIME

Incubation time	*Coombs' reaction*
1 hour	*negative*
1½ hours	±
2 hours	++
5 hours	+++

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3. *Antibody titre.*—The reaction is definitely positive when a serum concentration in excess of that of the red cells is utilized. Nevertheless, positive reactions may be obtained, although weaker, when serum is diluted two to four times. In such cases, the antiglobulin test will be stronger if a weak dilution of the antiglobulin is utilized. With serum dilutions over 1:4, the Coombs test is, as a rule, negative, whatever the dilution of the antiglobulin serum. The incomplete *cold* antibody of normal serum has a higher titre. In our laboratory, the mean titre of this antibody is 1:16.

4. *Dilution of the antiglobulin serum* (Table II).—A 1:4 dilution of Coombs' serum seems most suitable; nevertheless, the test is always positive at 1:8, 1:16 and nearly always at 1:64. Dilutions of 1:256 are seldom active.

TABLE II.—INTENSITY OF COOMBS' REACTION ACCORDING TO DILUTION OF ANTIGLOBULIN SERUM.

	Dilution of antiglobulin				
Individuals tested	*1:4*	*1:16*	*1:64*	*1:256*	*Commercially available Coombs' sera*
S.S.	++	+	+	neg.	neg.
B.J.	++	+	+		neg.
J.S.	+	+	±		+
M.M.	++	+	+	neg.	
R.A.	+	+	+		
P.L.	+	+	+		neg.
A.L.		+++			++
T.N.	++				+
P.J.	+				±
R.J.	++	+	+		±
G.E.	++				+
S.M.	+	±			

5. *Age factor.*—The antibody is not found in the serum of newborn babies; it has been identified in the serum of 14-month-old and 16-month-old infants.

6. *Thermal sensitivity* (Table III).—Like Dacie's antibody, the warm antibody is sensitive to heat. Heating the serum at 56° C. for 30 minutes causes the warm antibody to disappear; this thermolability is the result of either destruction or some modification of the antibody and not solely of the disappearance of complement, since addition of complement to heated serum does not modify the reaction.

TABLE III.—RESULTS WITH SERUM HEATED AT 56° C. FOR 30 MINUTES

Mixture	*Coombs' Reaction*
Normal serum + red blood cells	+
Normal *heated* serum + red blood cells	Negative
Normal *heated* serum + red blood cells + complement	Negative

7. *The warm auto-antibody and macroglobulins.*—We thought it of interest to compare the reactions obtained with ordinary antiglobulin and with an anti-macroglobulin serum we have prepared. Table IV shows the discrepancy in the results from four cases selected at random.

It should be noted that if anti-macroglobulin serum fails to agglutinate red cells sensitized with the normal warm auto-antibody, it agglutinates red cells sensitized with incomplete anti-D as well as cells sensitized with auto-antibodies of acquired hæmolytic anæmias. Our immunochemical studies on anti-macroglobulin serum will be published in a separate paper.[5]

TABLE IV.—TESTS FOR AUTO-ANTIBODIES WITH ANTIGLOBULIN SERUM AND WITH ANTI-MACROGLOBULIN SERUM

Individuals whose red cells have absorbed the antibody	*Reactions with antiglobulin serum*	*Reactions with anti-macroglobulin serum*
L.C.	Positive	Negative
P.S.	Positive	Negative
G.E.	Positive	Negative
G.T.	Positive	Negative

8. *Warm auto-antibody and compatible red cells.*—The warm antibody not only acts on the person's own red cells but is also capable of agglutinating compatible red cells. It is an *iso*-antibody as well as an auto-antibody.

9. *Effect of anticoagulants.*—The natural warm auto-antibody cannot be detected in plasma. Oxalate or citrate inhibits the reaction.

10. *Persistence in serum.*—When serum is left standing for eight hours at 37° C., mere traces of activity can be detected; 24-hour-old serum is devoid of auto-antibody activity.

11. *Relations between the natural warm auto-antibody and substances with similar serological characteristics:*

(i) *The warm auto-antibody and the Unger test.*—After the discovery by Morton and Pickles[6] that trypsinized red cells are agglutinated in saline by an incomplete antibody, Unger[7] applied the Coombs test to trypsinized cells in order to obtain a more sensitive method of detecting incomplete antibodies. The Coombs-trypsin test is far more sensitive than either the Coombs test or trypsinization alone. Unger's reaction has been used here in investigating the natural auto-antibody.

Much higher titres were found with it. Whereas a titre of 1:1 or 1:2 is usual with the simple Coombs test, titres of 1:64 were not uncommon when the same test was performed on red cells previously trypsinized. From this finding, one might conclude that the Coombs-trypsin test is a more sensitive means of detecting the natural warm auto-antibody, but such a conclusion seems unwarranted. The experiments described in the first part of this paper were repeated using the Coombs-trypsin test. Table V shows that the warm auto-antibody detected by the Coombs-trypsin test differs sharply in many of its characteristics from those detected by the simple Coombs test.

High titre, absence of any anti-H specificity, positive reaction with anti-macroglobulin serum, positive reactions with highly diluted antiglobulin sera, and resistance to aging are all characteristics which sharply differentiate the antibody detected in the Coombs-trypsin test from that described in this paper. It is to be noted that Jankovic,[8] working with a Coombs-trypsin test, has described a

TABLE V.—COMPARISON OF WARM AUTO-ANTIBODY DETECTED BY THE COOMBS TEST AND WARM AUTO-ANTIBODY DETECTED BY THE COOMBS-TRYPSIN TEST.

Characteristics	*Auto-antibody as detected by Coombs' test*	*Unger's test*
Titre	Weak (3:1 to 1:16)	Strong (1:32 to 1:64)
Action of anti-coagulants	Untraceable in plasma	Untraceable in plasma
Addition of AB blood group substances to serum	Neutralized	Not neutralized
Presence in newborn	Negative test	Test weakly positive in a few cases
Anti-H specificity	Probable	No anti-H specificity
Heating of serum at 56° C./30 min.	Destroys the antibody	Destroys the antibody
Reaction with anti-macroglobulin serum	Negative	Positive
Dilution of anti-globulin	Weak (1:4 to 1:16)	1:4 to 1:256 dilution often active
Effect of storage	Very sensitive to aging.	Detectable on 5-day-old serum

natural warm auto-antibody in the majority of normal sera tested. Bearing this in mind, we will term this serological component "natural warm auto-antibody, Jankovic type", as differentiated from the one we are describing here.

(ii) *Relations existing between normal warm A.A. and normal cold A.A. described by Dacie.—Study of the Unger test at 2° C.* Dacie[3] described the presence of a cold incomplete antibody in most human sera. (We are not taking into account, in this paragraph, the results obtained with the Unger test at 37° C.—warm antibody, Jankovic type. This will be dealt with below.) Striking similarities are found on comparing the properties and characteristics of Dacie's antibody with the properties of our warm antibody, namely: low titre; demonstration by strong concentrations of antiglobulin serum only; long incubation period; thermolability; inhibition by anticoagulants; negativity of test with cells sensitized by stored serum; and anti-H specificity. As regards so-called "anti-H specificity", we wish to emphasize that the warm auto-antibody—as well as the cold incomplete antibody—can be demonstrated in most A_1B sera, provided a potent antiglobulin serum is used; but reactions are always weaker in the A_1B group than in the O or A_2 groups.

We have tried to separate the warm antibody from the cold antibody. Differential absorptions showed that absorption of the warm antibody from serum leaves cold antibody activity intact, whereas absorption carried out at 2° C. abolishes activity at 37° C. A few normal sera exhibited normal cold antibody activity without warm antibody activity. The converse—presence of warm A.A. without cold A.A.—has been observed in a few *patients*. For example, patient M.L.'s serum shows normal warm A.A. activity but no cold incomplete auto-antibody. This patient had acute leukæmia. We will publish a separate paper[9] on our findings in hæmatologic diseases.

Unger's test has been used for detection of cold incomplete normal auto-antibody. Needless to say, after incubation at 2° C., red cells were warmed and then washed at 37° C., to reverse normal agglutination of trypsinized red cells which takes place at 2° C., before antiglobulin was added. (On several occasions, complete elution of cold antibodies on trypsinized red cells was not easily achieved. Such cases were discarded.) In the majority of cases, the Unger test was strongly positive. The serological property so detected is independent of any anti-H specificity. It is detectable in aged serum, it is not neutralized by addition of specific blood group substances to normal serum before incubation with red cells, and on a few occasions it has been found at a low titre in the newborn. Heating serum at 56° C. abolishes serum activity. Again, we face the question of possible identity between the component detected by Unger's test and Dacie's cold incomplete auto-antibody. It is our impression that they are different since their characteristics vary widely. The subject will be discussed later.

(iii) *The problem of anti-H specificity.*—In 1953, Crawford[10] demonstrated that the normal cold incomplete auto-antibody has anti-H specificity. The normal *warm* auto-antibody behaves similarly. Activity is readily demonstrated in O, A_2 and B subjects whereas A_1B group shows weak reactions. Negative reactions were encountered in only one out of six A_1B samples tested. On the contrary, when A_1B serum is incubated at 37° C., it has a strongly active *iso*-antibody (Table VI).

TABLE VI.—WARM AUTO- AND ISO-ANTIBODY IN A_1B GROUP

A_1B subjects	*Auto-antibody*	*Iso-antibody*
T.D.	+	+++
M.H.	+	+++
R.H.	+	++++

III. "AUTO-ANTIBODIES" IN NORMAL SERUM

Table VII summarizes part of present knowledge on so-called "auto-antibodies" in normal serum.

TABLE VII.—"AUTO-ANTIBODIES" IN NORMAL SERUM

37° C. Incomplete warm antibody demonstrated by Coombs' test.
Incomplete warm antibody demonstrated by Unger's test (Jankovic).
2° C. Complete cold antibody
Reversible agglutinin (Rosenthal)
Incomplete cold antibody (Dacie)
Incomplete cold antibody in Unger's test
Other antibodies
Agglutinin T of Thomsen and Friedenreich
Agglutinin P of Moskowitz and Treffers

Up to now, we have used the term "antibody" to describe serological components which may have nothing to do with immunological phenomena. It remains to be proven that these substances are

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the result of an antigenic stimulus. We now come to what seems to be the most important point.

IV. Is Normal Warm Auto-antibody a True Antibody?

We have demonstrated that incubation of normal serum with its own red cells at 37° C. renders these cells Coombs positive, provided a strongly anti-globulin serum is used. We have termed this substance "auto-antibody". That a positive Coombs' test means adsorption of an antibody on the red cells should not be accepted without question. Actually, Coombs' test shows the adsorption of a protein on to the red cell, which is not necessarily an antibody. When dealing with pathological antibodies, the reaction retains its high significance. Moreover, a positive Coombs reaction in such instances is but a part of a striking clinical picture. But in experimental work, when sensitization of red cells proceeds artificially, *in vivo*, with proportions of serum and cells that are probably never encountered physiologically (*a fortiori* when artifacts are introduced, such as the use of trypsin), too sharp a conclusion should not be drawn. We have undertaken a few experiments to evaluate the role of the normal auto-antibody in hæmolysis.

Mechanical hæmolysis. Red cells incubated with their own serum, in proportions already indicated, were subjected to mechanical hæmolysis by the method outlined by Ham.[11]

When cells were subjected to mechanical hæmolysis after incubation with their own serum previously heated at 56° C., for 30 minutes, hæmolysis was greater than when cells were incubated in their native unheated serum. This would seem to indicate that adsorption on to red cells of the warm auto-antibody would exert some protective effect. Likewise, when cells treated the same way were subjected to agglutination and hæmolysis by rabbit serum, hæmolysis was more pronounced with cells incubated in their own *heated* serum, whereas incubation in unheated serum seemed to protect red cells, to a certain extent, against hetero-hæmolysis. The evidence that warm auto-antibody is the protective agent is meagre and these experiments, which are still in the preliminary stage, need to be confirmed and extended. Nevertheless, they seem to indicate that the serological component we have termed *antibody* is not necessarily an agent deleterious to red cells and that a possible role of defence can be postulated for it.

Roth[12] has observed that under certain conditions eluates from red cells of patients suffering from acquired hæmolytic anæmia seemed to protect cells against spontaneous hæmolysis *in vitro* at 37° C. Dacie, in a recently published paper[13], considers that complement is very likely the serological component which reacts with cells having adsorbed cold antibodies. Facts and opinions corroborate the impression that much more precision is needed before a positive Coombs test on cells incubated with their own serum, either at 37° C., or at 2° C., can be definitely interpreted in terms of an immunological mechanism directly related to antibodies.

Discussion

We have demonstrated that in normal serum there exists an antibody of the incomplete type, acting at 37° C., on the subject's own red cells. This antibody is demonstrated by the indirect Coombs reaction, after a minimal incubation period of two hours, using red blood cell concentrations which should never exceed 10% if clear-cut reactions are to be obtained. The titre seldom exceeds 1:4 although in a few instances it has been as high as 1:16. Antiglobulin serum should be used in dilutions of 1:4 to 1:16. Negative results are obtained with an antimacroglobulin serum which seems directed against gamma-globulins only. The relationship of this serological component to the incomplete cold antibody of normal serum remains an open question.

Furthermore, we have applied the Unger test or Coombs test with trypsinized red cells to the study of the incomplete warm auto-antibody. Important differences have been found between results obtained with Unger's test and the simple Coombs test.

The immunological nature of the reported phenomena is not at all established. We may be dealing with one or more factors having more of a protective than a deleterious effect on red blood cells. However, keeping in mind the fact that natural warm "auto-antibody" and natural incomplete cold "auto-antibody" both detected by the antiglobulin reaction and the other serological components detected by the Coombs-trypsin test could be erroneously identified as abnormal antibodies, some practical conclusions may be drawn:

1. A two-hour incubation of serum and red cells is necessary when normal "auto-antibody" is sought, whereas a one-hour incubation is sufficient when dealing with a pathological antibody.

2. The proportion of serum in the sensitizing mixture must be predominant when in search of natural antibodies.

3. Normal warm auto-antibody is heat-sensitive, whereas pathological warm auto-antibody is not altered by heating. The same does not hold true for both normal and abnormal *cold* incomplete antibodies, which are affected by heating.

4. Most abnormal antibodies can be detected by relatively high dilutions of antiglobulin serum, whereas weakly diluted antiglobulin is indicated when dealing with normal auto-antibodies.

5. Consequently a pathological interpretation should not be attached to a positive Coombs test on cells which have been incubated with their own serum for more than 1½ hours, particularly when the proportion of serum in the serum and red cell mixture is predominant.

6. Unger's test—i.e. the antiglobulin test on cells previously trypsinized—does not possess any patho-

logical significance, unless the serum suspected of containing abnormal antibodies has been heated at 56° C., before incubation with the test cells. This does not hold true for tests performed at 2° C.

SUMMARY AND CONCLUSIONS

This paper reports the description of an "auto-antibody" active at 37° C. This serological component was found in 99% of the 150 normal sera tested. Jankovic's finding of a positive trypsin-Coombs test at 37° C., in every subject tested, is also confirmed. A similarly positive trypsin-Coombs test at 2° C. is reported. That this serological component is necessarily related to true immunological phenomena remains to be demonstrated. Caution should be exercised in the interpretation of a positive Coombs test.

Several interpretations may be brought forward to explain the presence in serum of such component or components. It is likely that they have something to do with the normal hæmolytic process, either on the positive or the negative side. It can also be postulated that abnormal hæmolysis may result from an imbalance in the highly theoretical auto-immunologic part of the mechanism of hæmolysis. The question still requires extensive research and thought. Striking results may be obtained some day, shedding light on the mysterious problem of physiological hæmolysis and its pathological counterpart.

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RÉSUMÉ

Ce travail comporte la description d'un auto-anticorps actif à 37° C. Cette propriété sérique se retrouva dans 99% de 150 sérums normaux examinés à cette fin. On y confirme l'observation de Jankovic d'une épreuve positive de Coombs sur des globules trypsinisés à 37° C., obtenue dans chaque cas. L'auteur rapporte aussi une réaction de Coombs semblable à la précédente mais positive à 2° C. Il reste cependant à démontrer que ce facteur sérologique est nécessairement relié à un véritable phénomène immunologique car il faut exercer une certaine prudence dans l'interprétation de la positivité d'une réaction de Coombs.

Plusieurs modes d'interprétation s'offrent pour expliquer la présence dans le sérum de ce facteur (ou sont-ils plus d'un?) qui semblerait faire partie du processus hémolytique normal par action positive ou négative. Il est également plausible de prétendre qu'une hémolyse anormale peut résulter d'un déséquilibre de cet aspect hautement théorique du mécanisme de l'hémolyse. Cette question demande encore beaucoup de recherche et de réflexion. Espérons qu'avant longtemps, des résultats probants jetteront un jour nouveau sur le mystérieux problème de l'hémolyse physiologique et sa contre-partie pathologique.

HYDRAMNIOS

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IN THE PAST FEW YEARS there have been a number of published reports on hydramnios as a specific obstetrical complication. Barry[1] writing in the *Irish Journal of Medical Science* in 1953 gave a startling incidence of maternal and fetal mortality in association with this condition, and warned: "It is a condition fraught with serious maternal and fetal risks. It always requires careful management and considerable investigation." In his series of 100 cases there were three maternal deaths and a fetal loss of 71%. Sixteen of these babies had no congenital anomalies and, he considered, had had some chance of survival. He pursued this aspect of the problem by advocating attempts to reduce the hydramnios by medical or surgical means.

In 1948 Mueller[3] reported 62 cases of chronic hydramnios from the New York Hospital with one maternal death due to pyelonephritis and a fetal mortality rate of 52%. There were eight normal babies who had died apparently in relation to the hydramnios, six in association with labour and delivery complications (e.g. prolapsed cord). He reported separately four additional cases of acute hydramnios with total fetal mortality, in only one of which the fetus was malformed. All had been treated expectantly after the diagnosis of hydramnios was made.

At the Boston Lying-in Hospital[4] in 1955 there were 145 cases (155 babies), with a fetal mortality of 50.97% (79 babies). Sixty-eight babies had congenital anomalies; eight lived but the remaining 60 died presumably of the anomalies. This study did not deal with the causes of death in 19 stillborn and neonatal deaths, except to state that five were non-viable.

In 1950 Macafee[2] reported from the Royal Maternity Hospital, Belfast, 147 cases with one maternal death due to postpartum hæmorrhage. Of 172 babies the fetal mortality was 55.5%; 75 babies apparently died of anomalies.

In 1955 Yordan[5] reviewed 198 cases at the Sloane Hospital for Women. His fetal mortality rate was 43.8%; 46 babies died of congenital anomalies, 16 were pre-viable and 5 premature, 20 died of unknown causes, and 9 deaths he related to delivery complications such as version and extraction.

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At the Royal Victoria Hospital, Montreal, from 1946 to 1955 inclusive there were 74 diagnosed cases of hydramnios with 79 babies. The fetal loss was 48 babies, or 60.75%. Death was due to congenital anomalies in 30, and seven were non-viable (Table I).

TABLE I.—CAUSES OF DEATH (R.V.H. SERIES)

Congenital anomalies	30
Non-viability	7
Intracranial hæmorrhage	5
Undetermined (congenital anomalies, not related)	2
Intrauterine asphyxia	3
Prematurity	1

Only one mother of the non-viable babies received antepartum care in this institution. She had twins with polyhydramnios of the second sac; the onset of labour was spontaneous at five months and one baby was living at birth. The remainder arrived at the hospital in labour at 6 to 6½ months; one mother was Rh negative without isoimmunization.

TABLE II.—LABOUR AND DELIVERY COMPLICATIONS (R.V.H. SERIES)

Retroplacental hæmorrhage	4
Prolonged labour	2
Inertia	4
Precipitate delivery	1
Postpartum bleeding	5
Curettage	2
Breech	3
Deflexion attitudes (military)	1
Hand presentation	1
Transverse lie	1

The mother of the premature baby was a diabetic; the onset of labour was spontaneous at seven months and the baby was born alive.

Loss of the other 10 babies appeared to be directly due to the hydramnios. Intracranial hæmorrhage was a postmortem diagnosis—two of these babies showed asphyxia pallida at birth, one delivered as a breech at home, one after a prolonged labour, and one by forceps for fetal distress in retroplacental hæmorrhage.

Anomalies of the extremities only were found post mortem in two babies. One had died in utero with marked polyhydramnios, and the other was a neonatal death after a labour where the membranes had been ruptured for a long period.

The deaths due to intrauterine asphyxia included a case of twins with marked polyhydramnios in the second sac and pyelonephritis in the mother. The last was a case of transverse lie with premature rupture of the membranes, version and extraction delivery.

The majority of patients (30) went into labour spontaneously between the 24th and 36th weeks. Twenty-three were induced between 28 and 36 weeks by medical and/or surgical methods.

In every instance the intrapartum bleeding began shortly after rupture of the membranes and continued until the placenta was delivered. All of the abnormal positions were in single pregnancies. One breech was delivered at home and died; another had multiple anomalies. The military deflexion attitude was in a baby delivered at term. The hand presentation occurred in association with an anomaly. The transverse lie was at term, with bleeding, version and extraction, and the infant was born dead.

A comparison of the reported labour and delivery complications (Table III) shows that these were similar for the various institutions but with some difference in numbers.

TABLE IV.—CONDITIONS SAID TO BE RELATED TO HYDRAMNIOS (R.V.H.)—(1946-55)

	Cases	*Hydramnios*
Diabetes	75	3
Toxæmia	791	4
Rh immunization	160	2
Multiple pregnancy	372	5
Monsters	125	22
Hydramnios	74	

Hydramnios is said to be related to a number of other obstetrical complications (diabetes, toxæmia, Rh immunization, multiple pregnancy). The total numbers of each of these conditions indexed for the past 10 years is compared in Table IV with the number showing hydramnios, and it is surprising to see how infrequently the two conditions were associated in this group. Hydramnios occurred most frequently with monsters, which of course do not account for all congenital anomalies.

In each pair of twins the babies were of the same sex, except in one pair and these had a mild degree of hydramnios only. The others all had polyhydramnios in the second sac. Three sets of twins perished.

At all institutions but the Sloane Hospital, parity was thought to be of significance (Table V). At the Boston Lying-in Hospital increasing birth order

TABLE III.—COMPARISON OF LABOUR AND DELIVERY COMPLICATIONS

	National Maternity Hospital	*Royal Maternity Hospital*	*Sloane Hospital for Women*	*R.V.H.*
Cases	100	147	194	74
Retroplacental hæmorrhage	7%	—	1.07%	5.41%
Postpartum hæmorrhage	13%	13.6%	2.45%	6.76%
Prolonged labour	—	—	4.8 %	2.70%
Inertia	10%	—	2.59%	5.41%
Deflexion	—	— (Brow)	0.4 %	1.35%
Transverse	—	—	0.4 %	1.35%

TABLE V.—COMPARISON OF ASSOCIATED FINDINGS

	National Maternity Hospital	*Boston Lying-in*	*Sloane Hospital for Women*	*R.V.H.*
Parity	P25/M75	—	—	P20/M53
Anæmia	—	9	—	41
Pre-eclampsia	13	24	32	5
Diabetes	—	4	5	3
Rh immunization	—	—	5	2
Anencephaly	—	34	—	20
Vaginal bleeding	—	27	—	3
Circumvallate placenta, partial	—	27	—	1
Other placental anomalies	—	11	—	3

was considered to be directly correlated with the appearance of hydramnios. The Royal Victoria Hospital patients with anæmia were those with a blood hæmoglobin value under 80%. All authors considered anencephaly to be the most frequent congenital anomaly, with a much higher incidence in females. At the Boston Lying-in Hospital vaginal bleeding during pregnancy was the most frequent associated clinical condition; there were 91 full pathology reports on placentæ, and the most common diagnosis recorded was that of partial circumvallate placenta. The Royal Victoria Hospital abnormal placentæ were all described in recent cases.

CONCLUSION AND SUMMARY

Hydramnios occurs most frequently from the 28th to the 34th week of pregnancy. Whether it is acute or chronic seems of less importance than its degree or severity. Hospital records show its being diagnosed at certain periods during a pregnancy but subsequent examinations do not note that it is increasing as the pregnancy progresses. The severe forms do not seem related necessarily to abnormal babies.

Radiography is of importance as a diagnostic aid, and has been used freely for this purpose in the Royal Victoria Hospital. Where the baby appears normal, the value of paracentesis in an effort to prolong pregnancy is firmly supported by some people and as firmly denounced by others.

Induction of labour by rupture of membranes and the use of Pitocin are the accepted methods, though a slow drainage of amniotic fluid may be more favourable to a normal baby.

RÉSUMÉ

L'hydramnios se manifeste le plus fréquemment entre la 28e et la 34e semaine de la grossesse. Sa marche lente ou aiguë compte moins que son degré d'intensité. Il n'est pas rare de voir dans les dossiers d'hôpitaux qu'un hydramnios découvert à un moment donné de la grossesse se soit stabilisé par la suite. Une grande quantité liquide n'entraîne pas nécessairement de malformations fœtales. La radiographie offre une aide importante dans le diagnostic de cette affection; elle est d'un usage courant à l'hôpital Royal Victoria de Montréal. Les opinions sur la valeur d'une paracentèse en présence d'un fœtus normal, dans l'espoir de prolonger la gestation, sont encore loin d'être unanimes. La rupture des membranes ou l'injection de post-hypophyse afin de déclencher le travail sont des méthodes généralement acceptées dans ces cas. Cependant une évacuation lente du liquide amniotique offre une meilleure chance d'obtenir un enfant normal.

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Case Reports

HEREDITARY HÆMORRHAGIC TELANGIECTASIA

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A HÆMANGIOMA is composed of a mass of blood vessels, atypical or irregular in arrangement and size. Varieties of hæmangiomata are distinguished according to the predominant type of structure. The plexiform angioma consists of dilated vessels which retain their ordinary form as coiled tubes and may be capillary or venous in type. The third type is the cavernous hæmangioma which is very similar to erectile tissue, consisting of large intercommunicating spaces lined by flattened vascular endothelium and separated by a definite but scanty stroma. These spaces usually contain fluid blood, but thrombosis may occur within them and phleboliths may even form.

The commonest site of these lesions is in the skin. Of the internal organs, they are most often encountered in the liver, less commonly in

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the spleen, gastro-intestinal tract, bone, kidneys and brain, and may be single or multiple. In cases recorded in the literature, multiple involvement of internal organs by benign cavernous hæmangiomata has occurred in various combinations.

Probably one of the earliest reported cases was that of Ullman,[1] who in 1890 described a cavernous type of hæmangioma lined by flattened endothelium occurring in the skin, liver, œsophagus, stomach, rectum and peritoneum. Since then many cases have been reported but few have shown such widespread visceral involvement as the case to be described. After a careful search of the literature, Blake and Lerro[2] found only eight instances in which histologically benign cavernous hæmangiomata were proved to exist in two or more of the internal organs. They added one case of their own, but in their review they did not include cases of primary involvement of the central nervous system, or cases where there was reasonable doubt of the benign nature of the condition.

Cavernous hæmangiomata in the lungs are usually localized lesions. Bowers[3] in 1936 drew attention to the lesion as an autopsy finding. The first clinical diagnosis of the presence of a pulmonary arteriovenous fistula was made by Smith and Horton[4] in 1939, but it was not until 1941 that Hepburn and Dauphinee[5] performed the first successful removal of an arteriovenous fistula by pneumonectomy. Since that time numerous cases have been reported, and Weiss and Gasul[6] were able to review 149 cases in the literature up to 1954. They deduced that over one-third of the cases had more than one lesion in the lungs, but none showed diffuse pulmonary involvement. Multiple lesions, when present, may be dense enough to appear on roentgenological examination of the chest, and may be associated with nævi of the skin and mucous membranes observed in hereditary hæmorrhagic telangiectasia, or Rendu-Osler-Weber disease. The etiology of this disease is unknown, but the tendency is probably transmitted as a dominant characteristic, both sexes being affected, though the familial incidence may not be evident in the individual case because of atavism.[7] The following case is recorded because of persistent, diffuse radiological findings, the true nature of which remained undiagnosed until autopsy was performed.

Mr. R.J.B., 80 years of age, was admitted to hospital at his wife's request because of marked senility, delusions of grandeur and increasing weakness, 13 days before his death. He was born in England, came to Canada at the age of 25, and served with the Canadian Army Service Corps during World War I. He received a pension for neurasthenia. In civilian life he worked as a farm labourer, and at no time did he give a history of exposure to dusty atmospheres. Both his parents lived to "old age", his father dying at 80 years of age, and his mother at 84. There were seven siblings, five of whom died in middle or old age, the precise cause of death being unknown; two are still living and well. There were two daughters by his marriage and both were described as having normal chest radiographs. The eldest daughter suffered from diabetes mellitus for two years and died of pneumonia at the age of 15. The youngest daughter was burned to death at the age of 23. She was married and had three children, one of whom perished with his mother. The other two are alive and well and have no cutaneous nævi or bleeding tendency.

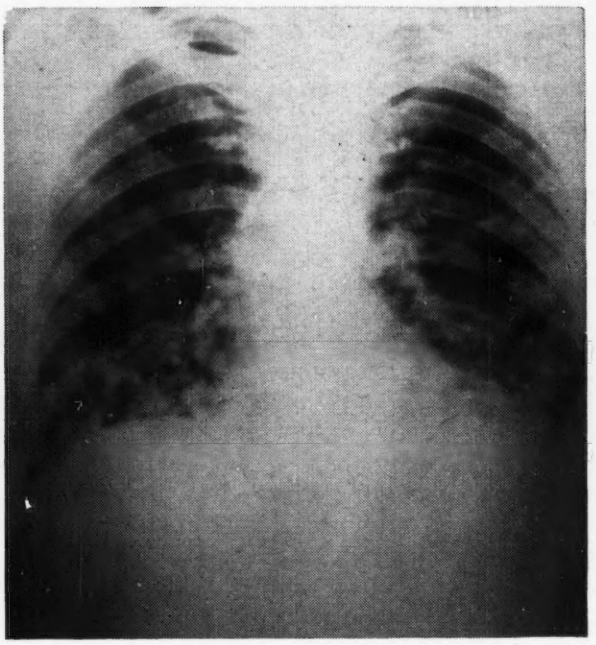

Fig. 1.—Chest radiograph of 1935 showing peculiar mottling of the lung fields. Films in 1946 and 1956 showed no further change.

In 1935, the patient underwent a pension medical examination in which the physical examination of the chest revealed nothing abnormal other than somewhat coarse breath sounds. However, fluoroscopy of the chest and stereoscopic films revealed throughout the lower two-thirds of the lung fields a coarsely mottled appearance produced by innumerable shadows of varying size and of rather heavy density. Fig. 1 demonstrates these chest lesions. The size of the shadows varied from 0.5 to 2.0 cm. in diameter. The first impression was that the picture was due to metastatic malignant deposits, but with the knowledge that these findings had been present in chest films since 1922, silicosis was considered. The distribution was not that usually seen with silicosis, but no definite explanation could be offered as to the etiology other than an atypical form of silicosis.

The patient was in hospital in 1946 with the complaint of increasing breathlessness on exertion for 10 years, but he gave no history of angina,

hæmoptysis, nocturnal paroxysmal dyspnœa or previous illnesses. Chest radiographs taken on this admission showed no changes in the pulmonary findings when compared with the films of 1935. Several dark purple nævi were noted in his skin, the majority of which were sessile and the largest measured 0.5 cm. in diameter. Two nævi in the skin of his right cheek bled occasionally after shaving, but those in the skin of his trunk were never known to bleed. There was one pedunculated nævus 1 cm. in diameter over the upper aspect of his right buttock, which had been present and of the same size "as long as he could remember". The only change noted in this nævus was that on compression it appeared to decrease to approximately half its original size. There was no mention of cyanosis and no recorded hæmatological findings on this admission.

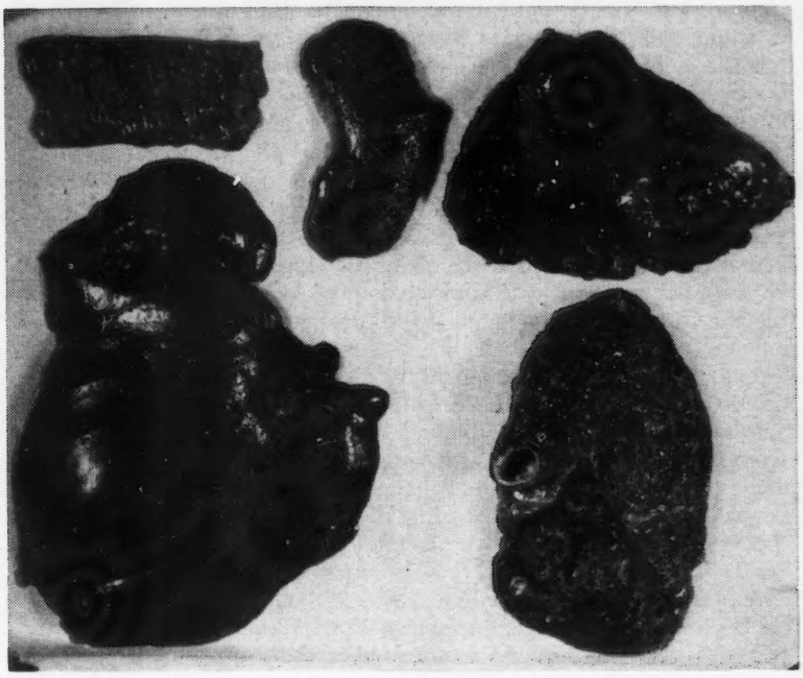

Fig. 2.—Multiple hæmangiomata as seen in the liver, jejunum, kidney, spleen and lung.

His second admission to hospital was in 1954. For the previous year he had become progressively more breathless on exertion and developed swelling of his ankles. Except for these presenting symptoms the functional enquiry was non-contributory and he denied any history of hæmatemesis, hæmaturia or melæna, though for the past three years he had noticed an unusual number of nosebleeds, the onset of which was spontaneous and unassociated with trauma. Clinically there was a moderate degree of pitting œdema of the legs, a blood pressure of 170/90 mm. Hg, and occasional fine crepitations at both lung bases. He had a normochromic normocytic anæmia, Hb. 66% (9.5 g. %), white cell count 6500 with a normal differential, E.S.R. 80 mm. in one hour (Westergren), and a reticulocyte count varying between 1.3 and 3.6%. The cause of the latter was obscure, for there was no definite evidence of blood loss though one stool specimen in a series showed a trace of occult blood. Hepatic function was also impaired, with a total serum protein of 7.9 g. (A/G ratio 4.4/3.5), cephalin cholesterol flocculation plus 2, thymol turbidity 8 units, and bromsulphalein retention of 21% after 30 minutes. He became negativistic, refused to cooperate for further investigation and was discharged from hospital on a daily dose of 1½ grains of digitalis, which appeared to control his peripheral œdema.

While he was followed up as an out-patient, progressive mental deterioration occurred and his final admission to hospital was in August 1956. Further chest radiographs compared with those of 1935 and 1946 showed no increase in size or number of the pulmonary lesions. While in hospital he refused food and drink, and was very difficult to manage; numerous epistaxes occurred. Laboratory findings were similar to those on his previous admission, with Hb. 66%, white cell count 5200, and impaired liver function. On the fourth day of his hospital stay he developed a fever and clinical evidence of a right lower lobe bronchopneumonia, which responded well to treatment, but his general condition deteriorated steadily and he died 13 days after admission to hospital.

Autopsy Findings

Postmortem dissection was performed 18 hours after death. The body was that of a normally developed white male, moderately well nourished and showing no evidence of peripheral œdema. Blue cutaneous nævi were noted; one group of three was situated in the subcutaneous tissues overlying the middle third of the right sternomastoid muscle and two small nævi were present in the skin of the right cheek. Other nævi were scattered in the subcutaneous tissues of the back and abdomen. One pedunculated nævus, 1 cm. in diameter, was present on the upper aspect of the right buttock. No nævi were observed on the mucous membranes of the mouth or nose.

Careful examination of the brain, cervical cord and meninges failed to reveal any nævi in relation to the central nervous system. On removal of the lungs from the thoracic cage, the pleural surface of both lower lobes, the right middle lobe, and the lower half of each upper lobe were mottled with innumerable dark blue nodular elevations. The right lung weighed 1400 g. and the left lung 730 g. These nodules were soft in consistency, and on incision collapsed with much oozing of dark red blood. The lung parenchyma was dark red in colour, and was made up of innumerable dark red, poorly defined nodules, the largest measuring 1.5 cm. in diameter. The intervening lung tissue showed a moderate degree of venous congestion, but no other lesion. The pulmonary artery and its branches were patent throughout and were of normal dimensions. The heart weighed 480 g. There was slight hypertrophy and dilatation of the left ventricle. Two small hæmangiomata were present in relation to the heart—one, 2 mm. in diameter, situated in

the adipose tissue immediately beneath the epicardium over the anterior aspect of the interventricular septum; the other, 4 mm. in diameter, beneath the endocardium on the left side of the interatrial septum.

No hæmangiomata were noted in the pharynx or œsophagus, but when the stomach was opened a number of small dark nævi were present in the gastric mucosa, the largest measuring 0.5 cm., and being of similar nature to those of the lungs, collapsing on incision with the oozing of dark red blood. Other hæmangiomata were present in the mucosa of the jejunum, ileum, cæcum, colon and rectum. Of all of these lesions in the gastro-intestinal tract, the largest was in the cæcum. It was flattened and measured 1.5 by 1.5 by 0.4 cm., and macroscopically appeared to be covered by an intact mucosa. There were two small hæmangiomata lying beneath the peritoneum covering the mesentery of the small intestine. The liver contained the largest lesion found in this case. It was situated on the anterior surface of the left lobe, measured some 3.5 by 4.5 cm. in area, and had a glistening membranous surface which was slightly umbilicated at the centre. Numerous other smaller lesions were scattered over the surface and throughout the parenchyma of this organ. The spleen weighed 550 g. This organ was tough and pale and contained numerous dark red nævi and thin-walled cysts containing clear fluid. The cut vessels stood out prominently and showed much atheromatous change and calcification of their walls. No hæmangiomata were detected in relation to the pancreas or adrenal glands. The kidneys were of normal weight, and lying beneath the capsule were many nævi. Incision of the renal parenchyma revealed that all these lesions were confined to the cortex and none could be demonstrated in the medullary pyramids. The renal pelves and ureters of each side showed no abnormality, but lying beneath the mucosa of the bladder were small nævi. Inadvertently, examination of the skeletal system was not performed. Fig. 2 demonstrates these hæmangiomata as seen in the various organs.

Histology

Microscopic examination of the hæmangiomata from the various sites recorded in the gross dissection shows them all to be of essentially the same structure. They are composed of large and small intercommunicating cavernous spaces containing fluid blood. These spaces are lined by a flattened vascular endothelium which shows no tendency to hyperplasia or malignancy in the many sections of these lesions examined. The flattened endothelium is supported by a thin fibrous stroma. However, there is a slight variation in the thickness of this supporting stroma, it being most prominent in the pedunculated lesion of the skin. Fig. 3 is a photomicrograph of one of the hæmangiomata in the lung. It shows the intercommunicating cavernous spaces formed by fine stroma lined by a single layer of vascular endothelium. No prominent small arteries or veins were demonstrated in association with these lesions, which are separated from each other by hyperæmic lung parenchyma, the alveolar spaces containing an eosinophilic staining œdema fluid. Fig. 4 shows a similar lesion in the kidney. The lesions in the liver have no tendency to form a false capsule at their periphery, and there is a moderate degree of fatty infiltration of the parenchyma of this organ, confined chiefly to the centrilobular regions.

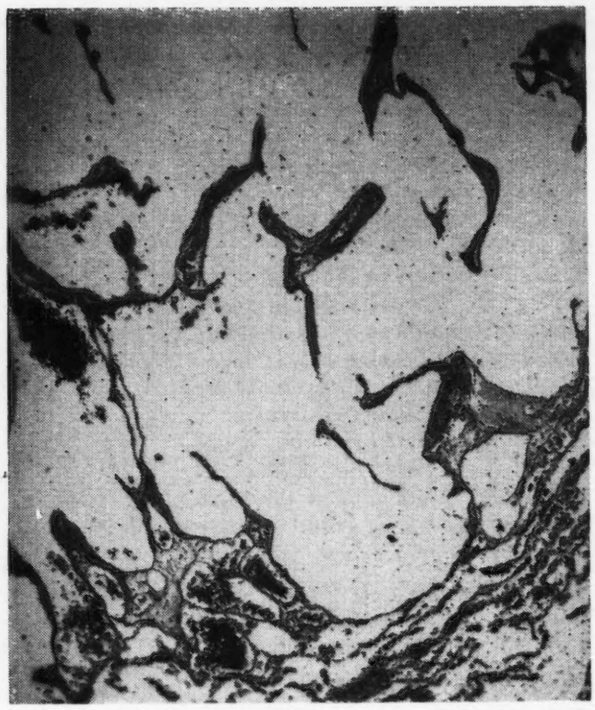

Fig. 3.—Photomicrograph of a cavernous hæmangioma of the lung.

DISCUSSION

This case was considered worthy of publication because no record of such diffuse pulmonary cavernous hæmangiomata, dense enough to

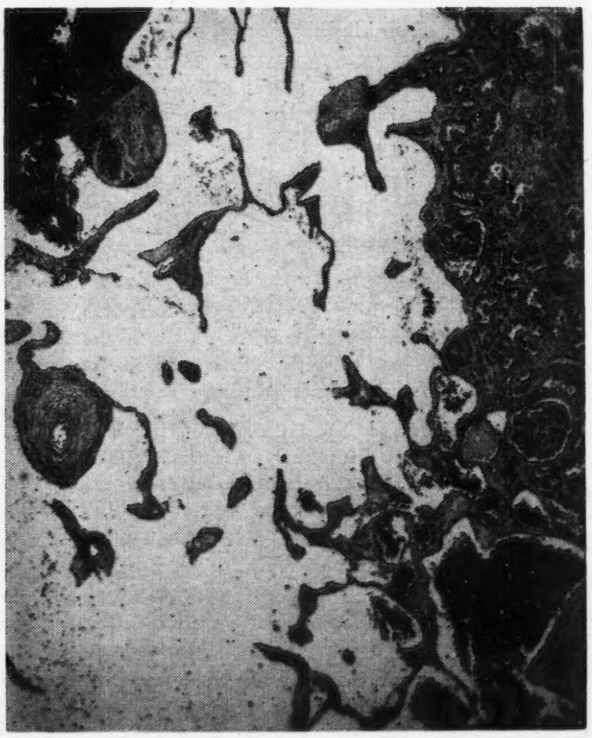

Fig. 4.—Photomicrograph of a cavernous hæmangioma of the kidney.

appear on a chest x-ray film, was found in any of the English or American literature to which I had access. The pulmonary lesions are also interesting in view of possible confusion with disseminated malignant disease involving the lungs. Unfortunately this condition was not diagnosed clinically and the chest was fluoroscoped only on one occasion, at which time no mention was made of pulsation in these lesions.

Cyanosis, hypertrophic pulmonary osteoarthropathy, polycythæmia and bruits over the chest were never noted, and there was no history of hæmoptysis or melæna. Epistaxis was the prominent symptom during the last five years of his life, and it must be presumed that this was caused by one or more small hæmangiomata within the nasal passages. The cause of the persistent normochromic normocytic anæmia was not proved clinically, but again it must be assumed that repeated small hæmorrhages were occurring from the gastro-intestinal and urinary tracts in addition to the overt epistaxes.

Neither his parents nor siblings had cutaneous nævi or a bleeding tendency, as far as is known. The two children by his marriage had no pulmonary lesions, no cutaneous nævi and no bleeding tendency, and these features are absent in his two surviving grandchildren. Thus no familial factors are demonstrable, though this condition must be diagnosed as hereditary hæmorrhagic telangiectasis as described by Rendu and Osler and elaborated upon by Weber.

SUMMARY

The unusual occurrence of multiple hæmangiomata of extensive distribution is the subject of this report. These lesions were particularly numerous in the lungs, occurring as incidental findings in chest radiographs, and also occupied most of the organs of the body, namely liver, spleen, gastro-intestinal tract, heart, peritoneum, kidneys, bladder and skin.

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BILATERAL AGENESIS OF THE KIDNEYS*

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IT HAS BEEN SUGGESTED that the anomaly of bilateral renal agenesis is more common than is generally believed.[1] However, it would appear from the reports in the literature that a case showing this abnormality, but with the presence of complete ureters bilaterally, is none too common. Other factors that make this case worthy of reporting are that the infant was a female, and that there were no other particular anomalies of the genito-urinary tract.

This baby girl was delivered on March 11, 1957, after a 35-week gestation period. The infant was difficult to resuscitate and remained quite cyanotic until death occurred 3½ hours after birth.

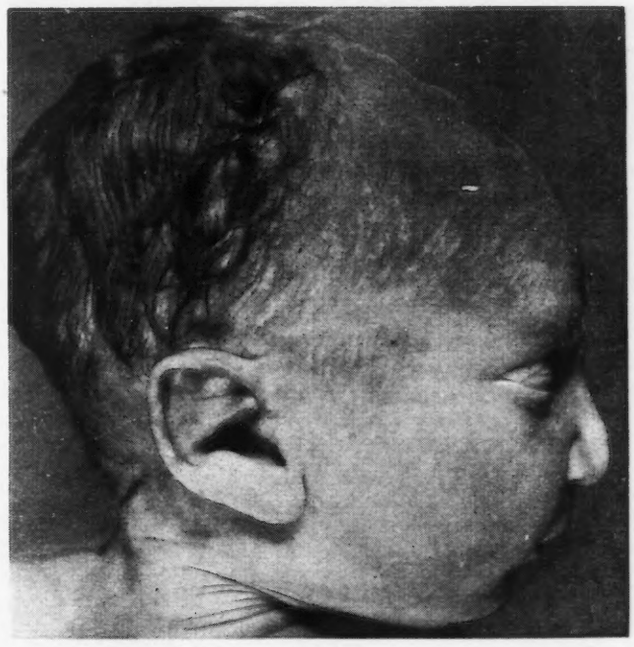

Fig. 1.

At autopsy no external abnormalities of the trunk or locomotor system were seen. The head and face presented some rather prominent characteristics (Figs. 1 and 2) which included a definite flattening of the terminal portion of the nose, a rather marked recession of the chin, and an increase in distance between the inner canthi of the eyes. The ears were also enlarged and very soft and pliable. No abnormalities were seen within the chest cavity. The gastro-intestinal tract was normal throughout. On examination of the posterior abdominal wall it was noted (Fig. 3) that both kidneys were completely absent. The ureters were present, extending to the lower edge of the rather large adrenal glands. The bladder was patent, and tubular in shape, and

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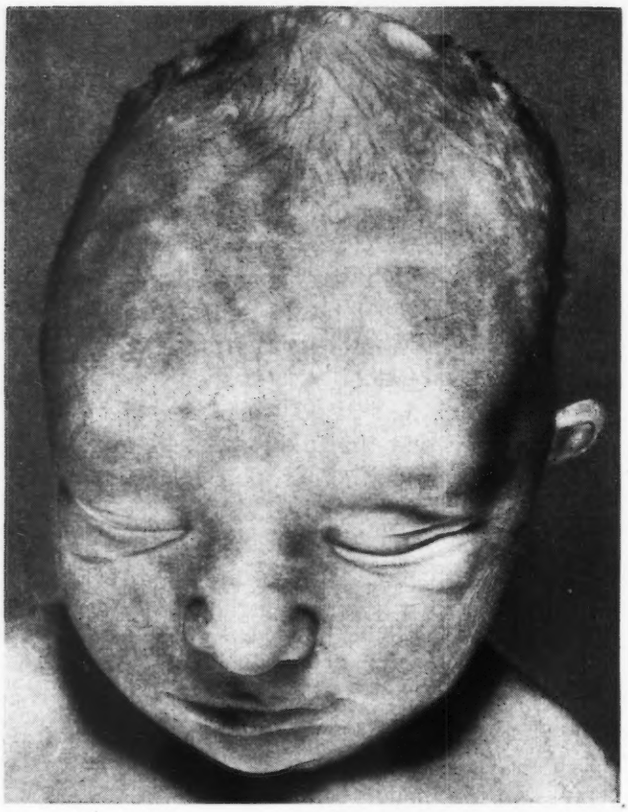

Fig. 2.

although smaller than normal revealed no other abnormality. The urachus was closed. The ureteral and urethral orifices were free from lesion, as was the urethra. No abnormalities of the ovaries, Fallopian tubes, or uterus could be found. There was a moderate dilatation of the vagina.

Microscopic examination of selected areas failed to reveal any suggestion of renal tissue. The lungs were atelectatic and markedly congested.

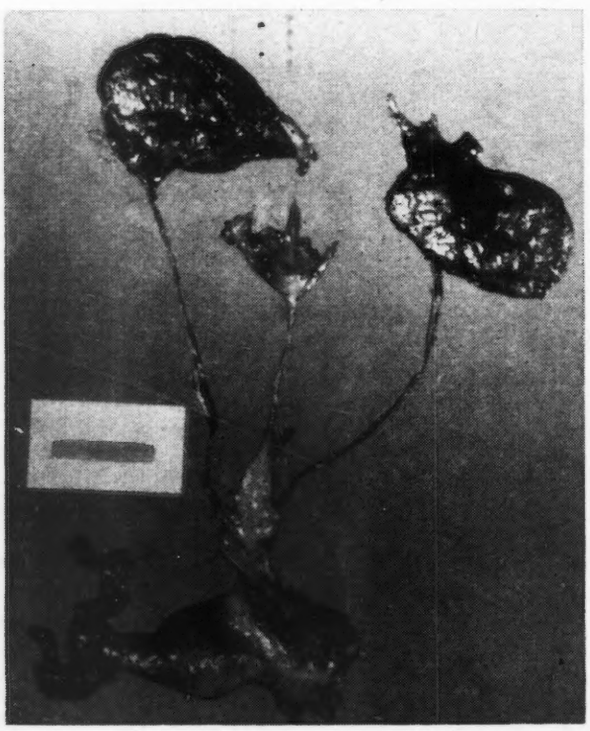

Fig. 3.

DISCUSSION

In a review of the literature (1954), Frumkin and Marz[2] stated that there were 166 reported cases, and added four of their own. Potter[1] reported that in 6000 autopsies performed on infants and fetuses at the Chicago Lying-in Hospital, there were 30 cases of bilateral renal agenesis. For no apparent reason this condition is more common in males, there being only four females in Potter's series of 30. Frumkin and Marz give a ratio of 3.07:1.

In a large percentage of reported cases there are other associated abnormalities of the urinary system. The ureters are stated to be usually absent, although portions may occasionally be present.[3] One of the most interesting features of this case was the presence of both ureters which extended up to the lower edge of each adrenal gland. A very careful search was made in this area for any tissue mass or aggregation that might possibly represent kidney tissue, but none was found. According to the literature[1, 4, 5] the bladder is usually anomalous. Complete absence, or at least marked diminution in size, is generally encountered. The bladder in the present case, however, although tubular in shape and somewhat diminished in size, was otherwise quite normal. The urachus was completely closed and the ureteral and urethral orifices appeared normal.

Abnormalities of the genital system are also the rule in the female cases reported. Often the uterus and vagina are completely absent, although the Fallopian tubes and ovaries are usually normally developed. In this case no abnormality could be found other than moderate dilatation of the vagina.

The extent of other concurrent malformations varies greatly in both sexes. This case was singularly free of such.

The characteristic facial features said to be associated with these cases are worthy of mention. Potter[1] noted (1) a flattening, softening, and enlargement of the ears, usually placed low on the head with a tendency to be less upright than normal; (2) a flattening of the tip of the nose; (3) a recession of the chin; (4) an increased space between the eyes; (5) a prominent epicanthic fold about the inner canthus of the eye. Certainly the facies are quite striking, and except for the last, all of the features outlined above were quite prominent in this case. However, similar findings are noted to be present in other renal anomalies, such as in polycystic kidney.[6] There are a number of reported instances[2] of renal agenesis in which these facial characteristics were not evident.

SUMMARY

A case of bilateral agenesis of the kidney is presented.

A short discussion of incidence and general findings in these cases is included.

Attention is drawn in this case to the presence of both ureters, and to the absence of associated congenital anomalies, especially in the remainder of the genito-urinary system.

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PARA-UMBILICAL RUPTURE OF THE LINEA ALBA, CAUSED BY ASCITES

A. R. H. OAKLEY, M.D., *Edmonton, Alta.*

A WHITE MALE, 65 years of age, was admitted to hospital for the first time with gross distension of his abdomen, caused by ascites. This distension was so great that the abdominal wall resembled a diaphanous covering—like a balloon inflated to its limit—giving the impression that it needed only the prick of a needle to burst the abdomen. The umbilicus itself was not unduly protuberant.

Immediate abdominal paracentesis was done, 18,000 c.c. (18 quarts) of ascitic fluid being drained away. The following day, 21,000 c.c. (21 quarts) were obtained, and the next day 11,000 c.c. The man was in hospital for nine weeks, and during this period a measured total of 72,000 c.c. (18 gallons) was aspirated from the abdominal cavity.

Two weeks after he was discharged, his abdomen "burst" while he was in bed, and he was again admitted to hospital. A witness, who arrived shortly after the calamity, stated that the bed and floor were flooded—as though a waterpipe had burst. It is probable that five gallons of fluid escaped through the rupture.

The arrow in Fig. 1 points to the rupture, which was in the right lower quadrant of the umbilical sulcus, and is here seen as a pear-shaped hole. The umbilicus has been pulled to the left, and the sulcus stretched to demonstrate the rupture site. Before this was done, it was impossible to determine accurately where the seepage of fluid was coming from.

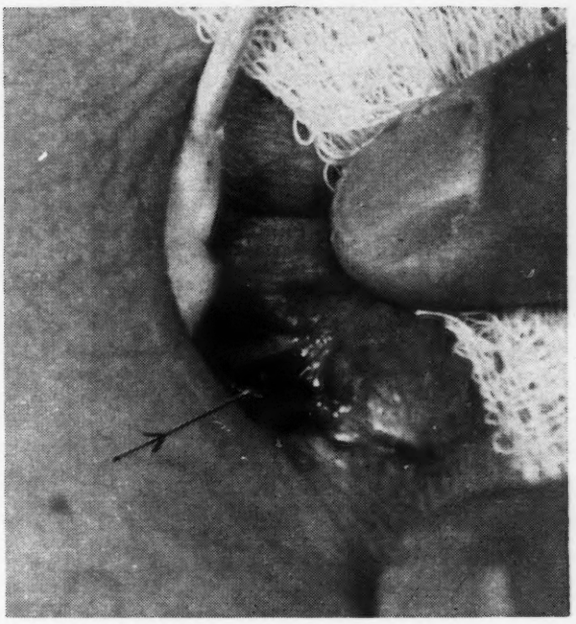

Fig. 1.

The rupture was a slit, about 1 cm. in length, with clean-cut, regular edges, and it was again noted that the umbilicus was not unusually prominent.

The man died three weeks after this second admission to hospital. Three days before his death the tear probably closed, as the umbilicus was dry for this period, and 2000 c.c. of fluid was present in the peritoneal cavity at autopsy.

Liver function and other tests indicated impairment of liver metabolism, which, with the clinical findings, indicated a diagnosis of *portal cirrhosis of the liver, with ascites.*

AUTOPSY REPORT

1. The umbilicus was markedly extruded, with no evidence of fluid seepage.
2. The peritoneal cavity contained approximately 2000 c.c. of brownish-yellow serous fluid.
3. A diffuse peritonitis was present, together with paralytic ileus.
4. The liver weighed 2200 grams (normal average 1750 g.) and its surface was nodular. Microscopically, sections showed a typical portal cirrhosis.
5. The spleen weighed 520 g. (normal average 200 g.). Microscopically, an unusual finding of extramedullary hæmatopoiesis—myeloid metaplasia—was present.

The cause of death was a diffuse peritonitis and paralytic ileus, resulting from a perforation of the umbilicus caused by ascitic pressure from portal cirrhosis.

COMMENTS

This case is an example of intra-abdominal tension causing rupture of the abdomen at the umbilicus, and could be classified as an internal tension rupture of the abdominal cavity. No record of a similar case has been found in the literature examined.

When the patient was first seen, it was noted that the umbilicus was not protuberant; neither

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was there any evidence of an umbilical hernia. It has been stated[1] that "In ascites, the umbilicus becomes everted, but this can only occur if there is a hernia at the umbilicus." This case confirms this statement.

The exact location of the rupture is interesting. Rupture might have been expected to occur at the usual common sites of para-umbilical hernias—just above (the commoner) or just below the umbilicus.

However, the potential weakness in this region is at the bottom of the umbilical sulcus, which is the external circumference of the base of the inverted umbilical stalk. Here, all that separates the peritoneal cavity from the exterior is the peritoneum and skin, with an intervening layer of sparse superficial fascia. The central core of the umbilical stump consists of scar tissue, and therefore offers more resistance to pressure than the periphery—the umbilical sulcus.

In the autopsy report, there is no mention of any abnormality of the "ligaments" converging on the umbilicus. It is possible that an unusual arrangement of the umbilical arteries, left umbilical vein or urachus was the underlying cause in producing a weakness at the rupture site, as Thorek[2] states that "The retraction of the umbilical vein usually draws the scar (umbilical) against the uppermost circumference of the umbilical ring; this is the weak spot where umbilical hernias may occur."

This man was extremely unco-operative. When first seen, he refused to go into hospital, and when he was discharged he was told to come to the office for paracentesis, but failed to do so. For his second admission, the help of the police had to be obtained.

It is hard to credit that anyone could voluntarily allow his abdomen to swell to such a size that it finally burst.

The absence of pain should be noted, as this is a constant feature of many comparable intra-abdominal uncomplicated swellings, such as a gravid uterus and ovarian cyst.

The quantity of fluid which the abdomen contained before spontaneous rupture occurred and the enormous amount excreted into the peritoneal cavity in this case are remarkable. It is estimated that, when rupture did occur, the abdomen must have contained at least 21,000 c.c. (5 gallons) of fluid. During a nine-week period, the total amount of fluid drained from the abdominal cavity was 72,000 c.c. (18 gallons). As a comparison with the quantity of fluid evacuated—the average hot water tank in a house holds 22 gallons, a household pail two gallons, and, probably more indicative still, the volume of the full-term gravid uterus[3, 4] is about 7000 c.c. (7 quarts, or almost 2 gallons). Taking the latter as a comparison, the abdomen, before rupture occurred, contained at least twice the volume of a full-term gravid uterus.

SUMMARY

A case of para-umbilical rupture of the abdomen, caused by ascites, is described. The ascites was due to portal cirrhosis of the liver. The reasons for the rupture occurring where it did are briefly discussed.

I wish to acknowledge my indebtedness to the Royal Alexandra Hospital, Edmonton; Dr. P. W. Davey, pathologist, the Royal Alexandra Hospital, for the autopsy report; Dr. R. E. Jespersen, Edmonton, for his help in the management of the case; and Mr. Z. A. Zielinski, medical photographer at the Royal Alexandra Hospital, for taking the photograph reproduced in this article.

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TESTICULAR TUMOURS

Surgeon Lieutenant Commander
J. E. SCHINBEIN, R.C.N., M.D., *Ottawa*

TUMOURS OF THE TESTICLE are uncommon, but occur with sufficient frequency to be important, especially as they are likely to be confused with hydroceles, as in the case reported below. The case is the first diagnosed at the Royal Canadian Navy Hospital, Esquimalt, B.C. This hospital and its out-patient departments see men practically exclusively between 18 and 45 years of age.

F.J., a 16-year-old cadet, was examined in his home city in July 1956, for admission to a Tri-Service College. He was passed as being physically fit but a small left hydrocele was noted and recorded. Two subsequent medical examinations before his arrival in the zone of this medical facility produced the same observation and diagnosis.

He was seen in sick bay because of a blow to the left testicle. The testicle was enlarged, hard and heavy but not tender. The mass did not transilluminate. It was felt that the mass was a tumour rather than a hydrocele or hæmatocele. There was no abdominal mass or left supraclavicular lymph node enlargement. Intravenous pyelography and chest radiographs were negative.

A left orchidectomy was carried out. The testicle was removed through an inguinal incision, the cord being tied at the internal ring.

The gross specimen revealed a greatly enlarged testis. After the tunica had been incised the tumour tissue bulged out; it was soft, friable, greyish tissue with areas of hæmorrhage.

The microscopic section revealed many large cells of one type showing numerous mitotic figures. The growth was moderately vascular. The diagnosis was that of an embryonal carcinoma of the left testis.

It was decided that this man should have a para-aortic lymph node dissection, followed by radiation therapy. He was transferred to his home city.

DISCUSSION

Testicular tumours are misdiagnosed or undiagnosed in 42% of cases. In 20% of cases they are misdiagnosed as a hydrocele. Metastatic lesions are present in 43% of cases on admission to hospital.

Tumours of the testicle can occur at any age but are commonest between 20 and 40 years, during the physical and sexual prime. Benign tumours of the testicle are rare. Malignant tumours are more prevalent in cryptorchism (11%). Any testicular enlargement should arouse suspicion of a tumour.

The diagnosis is made from the history and physical examination. The testicle should be handled gently to prevent dissemination, and transillumination should always be done. Serological examination should be done to rule out syphilis. An orchidectomy should be carried out rather than an incisional or punch biopsy. The spermatic cord should be tied off at the internal inguinal ring.

Metastatic lesions are diagnosed by finding an abdominal mass or enlarged supraclavicular nodes, or by intravenous pyelography and chest radiographs. The metastatic lesion is occasionally responsible for the presenting problem, with pain in the back, especially with an undescended testicle.

The Aschheim-Zondek test in the urine for Prolan A is helpful if positive. It may be strongly positive with a chorionepithelioma. A negative result does not rule out a testicular tumour.

Testicular tumours metastasize by the lymphatics through the spermatic cord to the para-aortic lymph nodes. These are located on the left side at the level of the renal pedicle. On the right side they are related to the vena cava at the point where the spermatic vein joins the latter. Spread can be unilateral or bilateral. These lymphatic channels join the thoracic duct, and tumour cells spread to the left supraclavicular gland of Virchow. Tumour cells may spread by the blood stream to the lungs.

The Friedman and Moore classification is generally used. This gives four fundamental structural patterns, alone or in combination, in the vast majority of tumours: (a) seminoma—35-45%; (b) embryonal carcinoma and chorionepithelioma—20-30%; (c) teratocarcinoma—25-35%; (d) teratoma—5%.

There has been confusion in differentiation between seminoma and embryonal carcinoma. The seminoma is more common in older persons. These tumours are slow-growing and metastasize late. They are very radiosensitive, with a cure rate as high as 90%.

The effect of radiation on embryonal carcinoma is not so predictable. The teratocarcinoma and chorionepithelioma are radio-resistant. These tumours metastasize relatively early, and have a low cure rate.

Seminoma is treated by orchidectomy and radiation. Chorionepithelioma has such a bad prognosis that simple orchidectomy is the only treatment indicated. Embryonal carcinoma and teratocarcinoma are treated by orchidectomy and retroperitoneal lymph node dissection. If there are one or two involved glands present, a bilateral dissection is indicated. In the presence of multiple glandular involvement, irradiation should be carried out.

COMMENT

A case of embryonal carcinoma without obvious metastasis is reported. The essential feature of this case is the misdiagnosis on three occasions of a hydrocele. The need for careful examination of the genitalia of all recruits is emphasized; any testicular enlargement must be carefully examined. This misdiagnosis is unfortunately reported frequently.

The seminoma without or with metastasis is curable by irradiation in a high percentage of cases. Embryonal carcinoma is best treated by retroperitoneal dissection and, if inoperable, irradiation.

SUMMARY

A review of testicular tumours is presented with incidence, lymphatic spread, classification and treatment. A case of embryonal carcinoma is presented, which was misdiagnosed as a hydrocele.

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Special Article

DOCTOR-PATIENT RELATIONSHIP OR DOCTOR-PUBLIC RELATIONSHIP

"Why don't you speak for yourself, John?"
The Courtship of Miles Standish—Longfellow.

"The lady doth protest too much, methinks."
Hamlet, III, 2—Shakespeare.

HARRY BAKER, M.D., *Vancouver*

A RECENTLY GRADUATED medical doctor may well be confused as to the status of himself and his fellow colleagues in the community. As an undergraduate he read about many doctors of the past. They were of varying levels of stature but each was an individual, judged by what he did. They worked as individuals. They were not necessarily agreeable people to work with, because often enough they were at odds with those about them. They certainly were not interested in whether people liked what they did. They did not care whether people liked them. They were made of sterner stuff. They were philosophers and thought about the many faces of nature.

Today we seldom find a philosopher among doctors. Scientific doctors there are, many, usually working in teams. The others in practice too readily accept what is given them by the scientists. In this pragmatic world, the tempo has been so speeded up that the practitioner has little chance to think things through for himself. Pressure is often brought to bear on him to prescribe the new remedy before the ink is dry on the newspaper which dramatically told of the new (yet unproven) discovery. All this may well be inevitable. It does not bring discredit to the medical practitioner. However, as a result of this he has become soft and vulnerable and fearful. He has become conscious of what people think of doctors. He has been told that it is important that he think about what people think of the medical profession.

The present-day practitioner seems to have forgotten that he is a better doctor than he ever was. He seems to have forgotten that he is standing on the shoulders of giants. The names of these great men go back to the beginning of recorded history when the healing art began. He seems also to have forgotten that there are many professions but his is the first in service. Yet for some reason or other the medical thinking today uppermost in the minds of many is "What do people think of me?" How has this happened?

PUBLIC RELATIONS

One of the by-products of modern advertising has been termed public relations. As a by-product it probably fulfils a need, a need which time has produced. When a business or industry is small, the buyer or consumer knows where to find the seller or craftsman. There is a personal contact. Misunderstandings may be readily cleared up or explanations made. When a business gets so big that the buyer or user cannot readily contact the responsible people in the firm, misunderstandings arise and ill will may be generated. The big business man realizes that there must not be too many dissatisfied customers — if he can do something about it. So he makes an arrangement whereby the customer can explain his grievance or have the article repaired or exchanged or explained. This phase of public relations is necessary and serves a good purpose.

There is another facet of the cult of public relations which is less desirable. Public relations tries to place the business man in a most favourable light in the public eye — this over and above that created by good, sound business practice. He is not only a good, honest business man who tries to satisfy his customers; they seem to say — "He is also very kind." "See how much he gives to charity." "See the fine circle of friends he has." "See what a great sportsman he is" — and so on. If this is what the business world wants, that is their affair. Maybe the big business man needs a bolster.

This thinking has no place in the practice of medicine, which is an individual activity even when practised in groups. For some reason the fallacy has arisen that doctors as a whole are the same as a big business and therefore have to be explained to the consumer public. For some reason some of the leaders in the profession have accepted this idea also. They have propagated the idea that the profession must be shown to the public to be made up of a number of kindly men who like to spend an evening on a public platform entertaining the public.

Every individual at least respects and trusts his doctor. Many love their doctor; but the general public no more likes the doctors of their community than they like the lawyers or the engineers or the plumbers or the undertakers. There is no reason why they should.

Leaders in the Canadian medical scene apparently believe that public relations techniques are worth while. They are using them to explain how the doctor works. Neither the doctor's work nor the doctor-patient relationship needs explaining. It cannot be explained. It is based on faith.

We are told by the men in the profession who favour the use of public relations personnel as a means of explaining the profession to the public, that doctors should come out of the "ivory tower".[1] I certainly don't know what they mean when they use this much abused cliché. I don't think they do either. Do they mean that the doctor should be a human being among humans? The doctor already is that. Do they mean that the doctor should take more part in the community life? Most doctors give readily of their free time in various community activities when their demanding duties permit them. What do they mean? Maybe they mean that the doctor studies too much and thinks too much in scientific terms. This could be. The doctor by his very work is an individual with a good intellect, who must know what he is doing. Could coming out of the "ivory tower" mean that the doctor should be so sympathetic with his patient that in a difficult situation he should lose his equanimity and look as worried and distraught as the patient's relatives? This would be foolish. The

doctor has to develop a poise which gives confidence even when the situation is at its worst. If he can't, he is of not much value.

We are told that all men are born equal. It follows therefore that it is not right that one man should appear more intelligent than those about him. If he does, he is not like the others. He is not one of the gang. Surely those who advocate that the doctors should come out of their "ivory towers" do not mean that the doctors should feign dulness of intellect to be more on a level with the population at large. I don't know. Doctor-patient relationship is an individual activity. While it is true today that there is often a third party in the form of a prepaid scheme, yet this third party does not play any part in the spiritual and professional relationship between doctor and patient.

On occasion, however, the doctor-patient relationship becomes confused and the other doctors in the community have to come into the picture. The doctor group may be called upon to heal the breach. This functioning doctor group may be called a grievance committee. It is wise to let the public know that there is available to the layman this means of airing his grievance. Conversely, the doctor group have banded themselves to help each other when in trouble. A medical protective group is generally not thought of as playing a part in the doctor-patient relationship. Yet it does, because it makes the doctor feel more secure, so that he functions better and gives better service. Another function of the doctor, as a group, in the doctor-patient relationship is the attempt to make one of their group more readily available in an emergency.

In the out-patient clinic the situation is reversed. Here the individual doctor acts as a representative of the doctor group and shows what calibre of man is the doctor. Here he is working not for gain. Out-patient work can be trying, and yet I feel that the doctors as a group are judged by their representative who works in the out-patient clinic. He must be gracious and understanding.

A medical column in the local press may be a useful means of serving the public. To serve the public is an end worthy in itself of a worthy profession. To try to mould public opinion for whatever end is of no value and unworthy of a noble profession. The column should be under complete control of the medical group. The only way to assure this is for the group to pay for the space.

There are occasions when a medical group in a community has to explain to the lay community why they have taken the stand that they have on a controversial subject. When this happens, the doctors should hire and pay for space in the local paper and not depend on a free news story to do it for them. In this way the medical group has control of the story and thus ensures its accuracy. A free news story may not.

The advertising world and the public relations cult forget that many of their ideas of the emotional activity of the individual and the group are directly derived from the psychological and psychiatric material taught to doctors in their training. This study is as old as medicine itself. There is no need for the loud fanfare for public relations in medicine which is so much in evidence today. Those who practise in Vancouver have seen how far publicity can go. The medical forums which have been held have roused the College of Physicians and Surgeons to criticize the methods used to advertise them[2]—and well the College might. It should have stepped in sooner. I don't know what activities about public relations there have been in other provinces.

Since September 15, 1955, there have appeared a series of articles in the *Canad. M. A. J.* under the collective title of "Public Relations Forum". The Public Relations Forum purports to tell us how to run our offices, how to behave in our offices, how to behave towards our patients, how to collect our fees, and so on. The material in the articles tells us nothing that an intelligent doctor does not know. The articles have on the whole been superficial. Some are more irritating than others.[3, 4] They could well be ignored without loss to the average reader of the *Journal*. In fairness, two of them were acceptable and made some sense.[5, 6] We are told at the beginning of the series that the writer of the Forum "being a layman is able to appreciate the points of view of both physician and patient".[7] Can only a layman appreciate the points of view of both physician and patient? From what has appeared in the Public Relations Forum it would seem that for some reason which I shall try to discuss later the Canadian Medical Association has set out to make us public relations conscious (whatever that means). This is part of the mechanism which presumably will help do the job. I have seen no discussion on this project of developing and selling the public relations cult to the medical profession. There has been almost no criticism of it. One excellent letter in the *Journal* has expressed the feelings of this paper succinctly.[8]

I said that one could ignore most of the articles in the Public Relations Forum without any loss. More recently the column has published a series of articles which would be amusing if their implications were not serious. These articles are based on a survey made for the American Medical Association by an independent research organization[9-12] to find out public attitudes towards the doctor. These articles will influence some doctors into thinking that a "scientific survey" of this type really is significant and means something. Nothing could be further from the truth. To top it off, in one of the following issues the Public Relations Forum goes on to analyze the figures brought out by the survey and attempts to draw "scientific" conclusions from them.[13] The only conclusion that makes any sense is one that we know already. People think more highly of their doctor than they do of the doctors as a group.

Maturity is a state of development towards which all thinking adults aspire. The mature individual does not have to think about it. He has arrived at this state in the normal course of events. The mature adult is not very much concerned with what people think of him. He is much more concerned with how he feels and what he thinks about what he is doing. So it should be with a mature profession like the medical profession. Let us look within ourselves, first individually and then as a group. But let us do it ourselves and let us judge ourselves not only as individuals but as trained individuals. Let us not be judged by people who have a mere smattering of the study of human nature.

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The generally accepted belief on our American continent is that all men are born equal. Therefore there must be a constant levelling effort! The public relations cult which is guiding our public relations program certainly must believe this. Why then do we find this in the Public Relations Forum? "But to urge people to acquire a family physician is not enough. Some mechanism must be set up through which people may make a wise choice of doctors on the basis of propinquity, age, sex, religion, etc. . . . "[13] These then are important criteria to use when choosing a family doctor!

We are told that a national prepaid medical scheme is coming. When this happens, we must be on our best behaviour or else the medical profession will not fare at all well. This would appear to be a very important factor for the interest in public relations by some medical circles. The *Canadian Doctor* has recently printed a short article which expresses this point of view. It shows how fearful some people seem to be of public opinion even when they have nothing to fear.

"The Canadian medical profession stands in imminent danger of being brought under a government scheme of health insurance on terms it may not entirely favor. The prevailing sentiment in Canada, as disclosed at reliable plebiscites, is toward the establishment of a comprehensive insurance scheme. If doctors want to secure the degree of consideration they would like and to which they are entitled in the planning of such a scheme, they must never cease their endeavour to improve their position in the public mind . . ."[14]

From the Public Relations Forum we get the same type of thinking. "That appears to be the state of affairs today. The non-medical individual is generally satisfied with his family physician, but highly critical of the amorphous mass he terms the 'medical profession'. The remedy is a sound public relations program, and I use the phrase 'public relations' in its composite sense. Public relations will promote the harmonious public relationships which the medical profession must have if it is to remain free to choose its own way."[7]

How this type of fearful thinking has arisen is hard to understand. Surely we can't all be this fearful and take this type of thinking seriously. What has the "public mind" to do with how our leaders act for us when the plans for health insurance are presented to them? Surely as a group we have leaders whom we can depend upon to see that we are dealt with fairly. What does the writer of the quoted paragraph mean when he says ". . . they [doctors] must never cease their endeavour to improve their position in the public mind"? Have the doctors been wicked men or dishonest men or cruel? How can the doctor today do a better job than he is doing? Never before has the public had such medical care.

Medical treatment has always been expensive, but to attain the standard of treatment expected today seems to be more expensive than ever. It may be difficult for some people to get treatment when they need it. The medical profession must help obtain adequate medical treatment for their fellow men. Some scheme to do this must be worked out and *it will be worked out,* but not if we use fear as one of the methods. With time and thought a scheme will evolve. It will be a fair scheme—fair to all concerned. With good leaders at our head, unafraid to state what good medical treatment entails, as doctors we have nothing to fear.

Difficulties will inevitably follow if when the time comes that those who lead us, those who speak for us, and those who write for us, believe and follow this tenor of fear as voiced in some of the recent writings in the medical literature relating to economics.

Doctors as a group are associated in everyone's mind only with unpleasant things. That is the only time anyone turns to a doctor, professionally—when he is in trouble. The patient loves his doctor because he trusts and has faith in his doctor. He knows that his doctor will always do the best he knows how. But doctors as a group are an abstract thing which one cannot get to know or get close to and somehow he cannot like the group.

This business of trying to please the public is not new. Let me quote from a recent paper in the *Vancouver Medical Association Bulletin.* The writer says this. ". . . Our problem is not as unique as we are inclined to believe, and in this connection I would quote the words of Dr. Robert Boal, President of the Illinois State Medical Society, delivered in 1882:

"The amenities of professional intercourse, and the obligations of medical men toward each other and the public, were perhaps better observed in 1850 than now. Then the doctor, next to the minister, was the trusted friend and counselor of every family to whom he ministered. He shared their joys, soothed their sorrows, and every passing year added to and cemented the attachment and affection between them. Now the doctor is regarded more in the light of a tradesman or mechanic, and is employed from the same consideration that a grocer, tailor or shoemaker is. The strong ties of gratitude and affection have almost ceased to exist. Relationship is now placed upon a mere commercial basis, and for this the profession is more to blame than the public'."[15]

Why Dr. Boal should have been so bitter about his fellow-practitioners in 1882 I don't know. One can go back much further and find that the medical profession as a group has never been popular. One obvious reason comes to the fore. In the layman's mind the doctor has always been associated with some of the unpleasantest things that have happened to him. People have to give vent to their feelings. One easy way to do it is apparently to make the doctor suffer vicariously in fantasy. So the doctor is a frequent butt of the layman's humour. This is true today as it has been in the past. It is so not only in everyday folk humour but in the arts and in the theatre. The doctor is expected always to have broad shoulders. So here also he must help carry some of the patient's burden. Doctors as a group might look upon all this as a form of mental catharsis for the problems of the people of the world. After all, more is expected of the professional than what he gives in his day-to-day work.

It is very interesting that medical public relations activity has been closely linked to the newspapers. For example, we are told that the medical forums held by the B.C. Division of the Canadian

Medical Association were conceived by one of the Vancouver newspapers.[16] On the whole this relationship between medicine and the newspapers is rather incongruous. The practice of medicine is thoughtful, careful and deliberate. It has to be. Newspaper work by the very sense of urgency inherent in it, is almost the opposite to this. It has to be. Knowing this, how closely can we associate our activities with the newspaper? Further we are told in the Public Relations Forum in the *Canad. M. A. J.* that "Accuracy is not absolute in the news story. It can't be. A news story, by necessity, is a distillation. It does not, it cannot contain every one of facts. The process of abstraction itself may appear to alter the content."[17] There may be some who fear that newspapers will ignore our activities. That would truly be a small loss. But no fear! Medical activity is always news. What we should fear is that the newspapers report about medical activity before it is ready to be reported. What we should fear is that our activity will be reported incorrectly. We should not expect free reporting for our benefit.

We are told in the Public Relations Forum that "doctor *must* co-operate with the press" . . . "because he has an obligation to the public as well as to his profession and himself."[17] What this means is hard to understand. To go on. There is then a quotation from a newspaper writer who says that people want knowledge about medicine and health and it must not be denied them.[17] It is even more difficult to know or understand the validity of this statement. If there is illness in a family, the doctor in attendance should be able to explain the situation to the patient or the relatives or both so that they know what is happening. If, however, some individual is truly interested in knowing more about science and medicine he can find much of value in the public library or the book store. Popular literature is not the place to get knowledge of this type.[18] I suppose some of this stems from the "do-it-yourself" trend. Surely this cannot be carried into self medical care.

Advertising people forget that doctors have much opportunity to learn how to get along with people. The earliest public relations guidance for doctors was laid down for us by Hippocrates. Through the ages doctors have learned to get along with their patients. Yet people who talk about doctor-public relations have the temerity to tell doctors how to do their work.

Does the medical profession need any special voice to speak for it? We everyone of us speak for ourselves every day in our daily work. Every day we give of ourselves in service to the public. If we go on to have too many varied means of showing ourselves to the public in a guise other than what the public expects of us, it may be said of us as did Hamlet's mother of the lady she was watching in the play, "The lady doth protest too much, methinks". There is no need for us to put ourselves in this position.

The title of this paper may be unacceptable to some who nevertheless may agree with varying amounts of the material discussed in it. They may say that there is no reason to suggest that we have to make a choice and pick one or the other. Through the ages as the doctor-patient relationship evolved, the doctor-public relationship also grew. Each plays its part today. The primary doctor-patient relationship plays the large important part. The secondary doctor-public relationship plays a relatively minor role. Because there is this intimate relationship between them, it follows that activity in one must influence the other. Present-day public relations techniques accentuate the doctor-public relationship and greatly over-emphasize its value.

The doctor-patient relationship is a healthy one. However, this attempt to raise up the very minor relationship out of all proportion to its worth must jeopardize the doctor-patient relationship because, as we said, a change in one influences the other. Discord will arise.

We must think clearly and objectively about this program of public relations we are being asked

(Continued on page 155)

SHORT COMMUNICATIONS

THERAPEUTIC TRIAL OF IPRONIAZID (MARSILID) IN DEPRESSED AND APATHETIC PATIENTS*

R. L. DEVERTEUIL, M.D. and
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THE FOLLOWING is a report on the results of a therapeutic trial made on a group of 31 psychotic patients, using iproniazid (Marsilid). This drug was originally introduced for the treatment of tuberculosis and other wasting diseases. It was found to produce, as a side effect in some cases, elevation of mood, increase in energy, heightened sensitivity to stimuli and other signs suggesting stimulation of the central nervous system.[1] It was known that the drug acted as a potent inhibitor of mono-amine oxidase[2] and caused accumulation of serotonin in brain tissue.[3] A recent hypothesis attempts to correlate this effect on enzymes with the stimulation of the central nervous system suggested by clinical observation.[4] Possible therapeutic value of the drug in states of depression or apathy has been discussed for several years, but systematic studies have been few and results inconclusive or conflicting.[5, 6] A recent paper which reports favourable results stresses that definite improvement occurred only in patients treated with iproniazid for longer than two months.[7] An average daily dose of 100-200 mg. has been recommended in most recent reports; however Scherbel, reporting on the beneficial effects of iproniazid on a group of arthritic patients, observed that the dosage could be reduced to and maintained at 10-15 mg. daily and that this dosage "has been found sufficient to maintain mental stimulation produced initially by a greater amount of the medication".[8]

*From the Verdun Protestant Hospital, Montreal. The authors wish to acknowledge with thanks the generous supply of iproniazid (Marsilid) which was provided by Hoffmann-La Roche Ltd. for the purpose of this investigation.

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A wide variety of toxic side effects of iproniazid has been reported from different sources, but information is inadequate and interpretation difficult. Among the more frequently mentioned and serious of these are: muscular hypertonicity and hypermotility, hypotension with dizziness and syncope, hepatitis (of five reported cases of hepatitis, none was definitely attributable to iproniazid), œdema, constipation and mental symptoms asociated with overstimulation of the central nervous system. In one study the side effects were sufficiently severe to require termination of treatment in five patients (out of 20).[7] Several reports warn of "withdrawal symptoms" and advocate a gradual termination of treatment.

The study reported here was an attempt made to gain experience in the use of iproniazid in a large mental hospital (1650 patients) where, following the striking benefits obtained with neuroleptic drugs, attention was turning to the vast numbers of patients, particularly those in whom depression of mood and activity were marked, who would reap no benefit from the new relief available to the anxious and excited patient, and for whom no drugs of comparable value were as yet available.

SELECTION OF CASES

A total of 31 cases were selected for study. The main criterion for selection was the presence of depression, with or without anxiety, or of apathy as a well-marked clinical feature, provided the investigators were able to establish that the patient's apathy was of primary defect nature and not a secondary withdrawal reaction resulting from anxiety.* Relatively little importance was attached to age (from 32 to 83), time in hospital (from 2½ months to 17 years) or diagnostic category (13 different types).

DOSAGE AND DURATION

All but four patients received 150 mg. daily in tablet form (50 mg. t.i.d.) for most or all of their period of treatment. The remaining four patients received 100 mg. daily (50 mg. b.i.d.). In 11 cases, dosage was reduced or treatment discontinued as a result of toxic reactions and eventually all cases in this study were taken off iproniazid, pending accumulation of additional data, as a result of the high incidence of toxic reactions and of one fatality. Because of this, there is a wide variety in the duration of treatment for different patients (14-112 days).

RESULTS

Of the 31 cases studied, irrespective of diagnosis, 11 (35%) showed a significant improvement. If five patients treated less than 15 days were omitted from this study, the percentage would be 42. In seven of the improved cases, the improvement was sustained and of good quality, in four it was mild or transient; five of these 11 improved patients were discharged and one died as a result of necrosis of the liver.

Three additional patients, not improved on iproniazid, were afterwards successfully treated with electroconvulsive therapy and discharged. On the other hand, six of the improved patients had been treated with electroshock before receiving iproniazid with unsatisfactory or inferior results.

In two female patients, the depressive reaction was converted during iproniazid therapy into a state of hypomanic excitement which subsided spontaneously when the drug was discontinued.

SIDE EFFECTS AND COMPLICATIONS

This study was characterized by a high incidence (35%) of side effects. Dizziness, loss of muscular tonus, and ataxia, with or without hypotension, occurred in seven, resulting in frequent falls which in one young woman led to a fracture of the tibia, while cerebral thrombosis was suspected in one man and another man was investigated for an expanding intracranial lesion because of these symptoms, which persisted as long as the patient was continued on iproniazid. Syncope was observed in two patients and asymptomatic hypotension in one. A fatal necrosis of the liver occurred in one patient. It is noteworthy that this was one of the four patients receiving the smaller dosage schedule of 100 mg. daily, and that the dosage was reduced to 50 mg. daily (because of her improvement) 14 days before the onset of jaundice, when the drug was immediately discontinued. The patient was put on bed rest, special diet, special nursing care and cortisone, but her condition worsened rapidly and the hepatitis progressed to a fatal necrosis of the liver in a period of 12 days.

At autopsy, no other lesion was found, the liver necrosis being of the type sometimes seen in response to toxic agents. A study of this case, and of two others showing a hypotensive reaction to iproniazid which occurred only several weeks after the drug was started and persisted and progressed for two to three weeks after decrease or withdrawal of the drug, suggests that some side effects of the drug may be delayed and cumulative, a possibility which has not yet been sufficiently stressed. Unfortunately, not enough time was available to study the value of a much smaller maintenance dose of iproniazid, as advocated by Scherbel.[8]

DISCUSSION

Our results in 35% of patients showing significant improvement with iproniazid could be questioned because they were not obtained under double-blind conditions. In previous publications from this hospital, some inherent difficulties in any clinical double-blind experiment have been

*It has been our experience that a number of patients whose behaviour is characterized by apathy respond well to chlorpromazine or other neuroleptic drugs, and in these cases we assume that the patient's withdrawing and apathetic behaviour served as an active defence against intolerable anxiety produced by life stresses.

pointed out.[9, 10] Our conviction that the improvement we saw was in most of the patients the therapeutic result of iproniazid treatment is based on the fact that most of the improved patients had served as their own controls, not having shown any favourable response to other therapies before iproniazid administration. All of these patients were well known to the investigators, and coincidental improvement or recovery as an outcome of the natural history of the condition could in most cases be ruled out.

At the risk of emphasizing well-known facts, it should be noted that this is not the first drug which has proved successful in the treatment of depressive conditions. The amphetamines, nicotinic acid, the barbiturates, testosterone, and other steroids, to name a few, have all been reported and used as effective therapeutic agents in depressions. At this time, there still exists no specific pharmacological therapy for depressive states or any other treatment that can be compared in prompt and general effectiveness to electroconvulsive therapy.

There would appear to be good reasons why the term "energizing drugs", which has recently been proposed for iproniazid and drugs with similar action, should not be permitted to become a stock phrase in the physician's vocabulary. Such a term would imply that all that is wrong with a patient in whom such drugs would be effective is a loss of vital or "psychic energy". The scientific authenticity of such a concept is, however, still questioned and psychiatrists who are accepting it have not yet come to an agreement with regard to an unambiguous definition of the term. The term "energizer" carries a deceptive notion that in depressed conditions energy is reduced, while in reality the situation is more complex and the maintenance of the inhibitory state which we observe clinically as a psychic depression involves a considerable expenditure of biological defence reactions to stress. In the new field of psychopharmacology, special caution is indicated to avoid seductively simple "explanations" which may be suggested by plausible terminology. The terms "tranquillizing", "ataractic", and "energizing" all ascribe to these drugs the value of producing a simple and predictable change in the organism. In fact their action is far more complex and less dependable than is implied in the use of such terms, and in the interest of a sober, professional attitude and of objective scientific thinking, it would appear advisable to avoid all terms which carry subjective value connotations and insist on less persuasive but more precise and neutral terminology.

The theory that mental stimulation is closely related to an increase in cerebral serotonin is attractive but has not yet been confirmed, nor is there any evidence that the fluctuations of serotonin contained in the brain are causally related to corresponding changes in mental function. Iproniazid is a powerful inhibitor of the enzyme mono-amine oxidase which is responsible for destroying serotonin in the brain. The amphetamines and drugs related to iproniazid, e.g. isoniazid, have also an inhibitory effect on mono-amine acids, but it has been claimed that they are less effective in this respect than iproniazid and hence less effective therapeutically in depressive conditions. In this connection, it should be noted, however, that Salzer and Lurie[11] observed with isoniazid a considerably higher percentage (68.3%) of good therapeutic results in depressed patients than we did.

Whatever its mode of action, iproniazid in our experience has proven effective in counteracting depressive symptoms. In certain cases, it was even effective after electroconvulsive therapy had failed. It seemed to hold particular promise in chronic and otherwise refractory cases which often presented a particularly difficult therapeutic challenge. The frequency of undesirable and serious side effects in our small sample at the recommended dosage, however, was high enough to deter us from continuing its use, at least until a sufficient amount of data has accumulated to determine the true incidence of serious side effects in a large sample.

SUMMARY

Iproniazid (Marsilid) was used in the treatment of 31 patients in a mental hospital.

The dosage used was 50 mg. three times a day (27 patients) or 50 mg. twice a day (four patients) over periods from 14 to 112 days.

The drug proved effective in counteracting depressive symptoms even in some cases where electroconvulsive therapy had failed. Thirty-five per cent significant improvement was obtained.

Side effects and complications consisted in dizziness, ataxia, loss of muscular tonus, hypotension and syncope. One patient sustained a fracture of the tibia in a fall due to ataxia. One patient died from acute toxic necrosis of the liver.

A theory concerning the mode of action of iproniazid is discussed, and attention is drawn to other pharmacological agents reported successful in the treatment of depressive conditions.

Iproniazid appears to be a drug with an interesting therapeutic potential in depressive conditions. At the present time the authors have discontinued its use because of the high incidence of serious complications in their small sample group.

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INDICATOR-DILUTION CURVES IN CARDIOVASCULAR DIAGNOSIS

If an indicator substance, such as dye, be injected into the venous circulation, its changing concentration in the arterial circulation can be followed by repeated sampling of the arterial blood. An indicator-dilution curve can thereupon be constructed by plotting concentration time after injection.

Such a technique has been used in the measurement of cardiac output and blood volume for many years. For the former computation, it is only necessary to know the quantity of dye injected and its mean concentration in the blood over the period of sampling. For example, if 20 mg. of dye is injected and the mean concentration of dye over a period of 30 seconds is 10 mg. per litre, this amount of dye must have been diluted by two litres of blood in 30 seconds, or by four litres of blood in one minute. The cardiac output is therefore four litres per minute. A similar type of calculation can be applied to the determination of total blood volume.

Despite the relative simplicity of the method, it is only within the past few years that the indicator-dilution technique has begun to enjoy the popularity that it deserves. Three factors have contributed to this situation. First, and the most important, the development and adaptation of suitable oximeters has enabled us to detect *and continuously record* changing concentrations of dye in circulating blood without the necessity of laborious chemical or colorimetric procedures. Secondly, the search for suitable indicator dyes has been rewarded by the discovery of T1824 (Evans blue), and more recently of a tricarbocyanine dye (Fox green), which has even more satisfactory light-transmission and light-absorption properties. And finally, the increasing degree of impunity with which surgeons are able to attack the heart has rendered it increasingly urgent to utilize every possible means to increase our accuracy in the anatomic diagnosis of congenital and acquired heart disease.

A normal dye-dilution curve, as detected by a suitable oximeter and recorded by means of a galvanometer, consists of a sharp rise in concentration, reaching its peak about 10 seconds after injection; a steep fall as the "bolus" of dye rapidly passes the sampling site; and a second and much smaller rise in concentration, as dye that has completed a single systemic circulation *repasses* the sampling site. Several groups of investigators, notably those at the Mayo Clinic and the Toronto General Hospital, have expanded the indicator-dilution technique to the point at which it now constitutes a relatively simple, flexible, and highly revealing method of study of the circulation in health and disease. This state of affairs has been the product of careful study of dilution curves resulting from the usual peripheral-vein injection method, the combination of the indicator-dilution technique with cardiac catheterization, and the intensive application of the principle of two-site sampling. For example, the typical low-output curve seen in congestive heart failure, severe mitral stenosis or "shock" due to myocardial infaction, reveals a slow appearance time and build-up time, a low peak, a slow return to base-line, and an extremely low or absent recirculation peak. After medical or surgical measures have been taken to correct the abnormality, the dye-dilution curve returns to normal.

Congenital heart disease with abnormal communications between cardiac chambers and great vessels is associated with right-to-left or left-to-right shunts or both. In left-to-right shunts, pulmonary blood flow is increased by the recirculation of blood through the lungs via the defect. The dye-dilution curve is decreased in amplitude because of the increased amount of blood in which the dye is diluted by reason of such recirculation. The disappearance slope is also greatly prolonged because of the prolonged recirculation of the dye-blood mixture through the lungs. An "early recirculation hump" may appear on the downstroke of the curve. In right-to-left shunts a portion of the dye passes early across the defect into the systemic circulation and arrives at the systemic sampling site earlier than that portion which has travelled the longer normal circulatory pathway through the lungs. The dilution curve thus has a characteristic double-humped contour with an abnormal deflection superimposed on the build-up portion of the curve.

By the combination of the indicator-dilution technique with cardiac catheterization, the *actual site* of such shunts may be confidently predicted. For example, in the case of a ventricular septal defect, if the dye is injected into the main pulmonary artery (i.e. distal to the shunt) via a cardiac catheter, the dilution curve is normal. However, if the catheter tip is in the right ventricle (i.e. proximal to the shunt), the characteristic contour of a right-to-left shunt is obtained. Numerous modifications of this technique, involving conven-

tional or retrograde catheterizations of cardiac chambers or great vessels, render it possible to localize defects between such cardiac chambers or great vessels with a high degree of accuracy.

It must not be forgotten that congenital cardiac defects tend to be multiple rather than single. For example, atrial septal defects are frequently associated with partial anomalous drainage of pulmonary veins into the right atrium. The usual situation is one in which pulmonary veins drain from the right lung only into the right atrium. In such a case, separate injections of indicator into the right and left pulmonary arteries, with the usual systemic sampling, will clarify the situation. The dye-curve inscribed after injection into the left pulmonary artery will be normal, while that from the right pulmonary artery will be abnormal.

Many techniques have been devised and discarded, in an attempt to detect and quantitate valvular regurgitation. At present the major problem is undoubtedly the demonstration and assessment of significant mitral regurgitation in the presence of mitral stenosis. Since no uniformly satisfactory surgical procedure as yet exists for the correction of mitral regurgitation, this question is frequently a critical and crucial one. At present it seems to be best answered by a combination of left-heart catheterization and an indicator-dilution technique involving two-site sampling. Various technical modifications exist, but all these involve the instillation of dye into the left ventricle with sampling both from a peripheral site *and from the left atrium.* In the absence of mitral insufficiency, a normal dye curve is inscribed at the peripheral sampling site, while *no* curve is recorded from the left atrial site. When mitral insufficiency complicates an obstructive lesion, a dye curve of greater or lesser magnitude is recorded from the left atrial sampling site. Various investigators are at present engaged in careful work in an attempt to derive formulas whereby the degree of reflux may be quantitated.

Many additional applications of the indicator-dilution technique could be described. Enough has been said, however, to suggest that a forward step of the first magnitude has been taken in the accurate anatomic diagnosis of congenital and acquired heart disease. It remains only to add a note of caution. As one becomes increasingly adept in the application of such techniques and the interpretation of their results, one tends to regard them as the *sine qua non* and the last court of appeal in the solutions of diagnostic puzzles. But pitfalls of this method do exist, and it is best looked upon as an adjunct to existing diagnostic procedures rather than an end in itself. S.J.S.

Editorial Comments

PREVALENCE OF HYPOTHYROIDISM

Abnormalities of thyroid function have always provided, and will probably continue to provide, an inexhaustible source of diagnostic disagreement among physicians. Naturally, it is not the gross examples of altered function in either direction that are usually misdiagnosed; it is the borderline cases that frequently escape detection. Hypothyroidism is, of course, less likely to be missed where this condition is endemic, as in the great "goitre belts" in certain parts of the world, such as Switzerland, India and the midwestern states of the U.S.A.

Borderline hyperthyroidism and hypothyroidism may at times have been overdiagnosed rather than the reverse. There are many patients whose natural sluggishness has been unsuccessfully treated with thyroid extract on the basis of an equivocal basal metabolic rate determination. Conversely, there must be a large reservoir of patients with thyroidectomy scars, whose only claim to such surgical distinction (or lack of it) has been an anxiety neurosis. It is somewhat interesting, therefore, to note the suggestion of Jackson[1] that in one of the most goitrous areas of the U.S.A. in which hypothyroidism is the most frequent chronic affliction, many cases still go unrecognized. This may be the result of too much reliance on a single basal metabolic test. It is suggested that such a test rarely registers "lower than it should", in contrast to frequent false-high readings.

One must perforce agree that basal metabolic tests are notoriously unsatisfactory unless carefully done, and that even then the results must be interpreted in the light of clinical findings. However, in doubtful situations, one may have recourse to the determination of serum protein-bound iodine or of the radioiodine uptake of the thyroid gland; and it now appears unnecessary to institute treatment of derangement of thyroid activity in either direction on the basis of tenuous or otherwise unacceptable evidence.

Despite the lack of agreement with regard to overdiagnosis and underdiagnosis between endemic and nonendemic areas, there are nevertheless two valuable and important observations offered by Jackson's paper, which are probably unfamiliar to physicians in whose practices hypothyroidism is a rarity. The first is that in hypothyroidism one of the most frequent complaints is of daily headache. Dramatic relief of this symptom occurs when the hypothyroidism is corrected. The second is that most preparations of desiccated thyroid lose their potency in three months, while others, though fresh, may be unreliable and of doubtful value.

To these may be added a third, described by Houston[2] on page 108 of this issue. This author shows that the myxœdema reflex described by Woltman can be a potent weapon in the diagnosis of hypothyroidism in general practice. Houston's article is certainly required reading for the general practitioner, who might be well advised to carry his reading a step further and study Asher's paper[3] on "myxœdematous madness", in which he shows that hypothyroidism may simulate mental disorder.

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TUBERCULOSIS IN HOUSEHOLD PETS

As a consequence of the falling mortality and morbidity rates in tuberculosis, it has become important to explore every possible avenue that may lead to its eradication as a disease of endemic status and of public health importance. One of these explorations has led to the suggestion of isoniazid therapy for persons in whom the tuberculin reaction has recently converted. Another is inexorably forcing a reconsideration of present policy regarding mass B.C.G. vaccination.

A less well explored subject has been that of the possible contribution now being made by tuberculosis in dogs and cats to the general pool of infection. It has been known for 50 years that tuberculosis caused by the human bacillus has a significant incidence in dogs, while in cats the infecting organism is usually bovine.

A two-part study[1] was recently carried out by a physician-veterinary team, the results of which are extremely interesting, if not actually startling. In an investigation of one-half of the human contacts of 14 tuberculous dogs, nine were found with significant tuberculous lesions, three requiring early antimicrobial therapy. Conversely, when the dogs and cats owned by 37 patients with active tuberculosis were examined, *Mycobacterium tuberculosis* was recovered from swabs of the alimentary tract of two dogs and two cats.

While the latter finding may merely indicate ingestion of tubercle bacilli by these animals, and their passage through the alimentary tract, this is not necessarily so, and in any case it does not detract from the importance of the converse finding of active tuberculosis in both human and canine members of the same households.

As the yield of new active cases of tuberculosis from standard case-finding procedures and programs becomes smaller, it is our duty to utilize every possible method of discovery of this disease, even though apparently costly and impractical at first glance. Only thus will we be able to hunt down and clear out the most obscure but still significant reservoirs of the disease. Further pursuit of this surprisingly promising line of investigation is therefore urgently indicated.

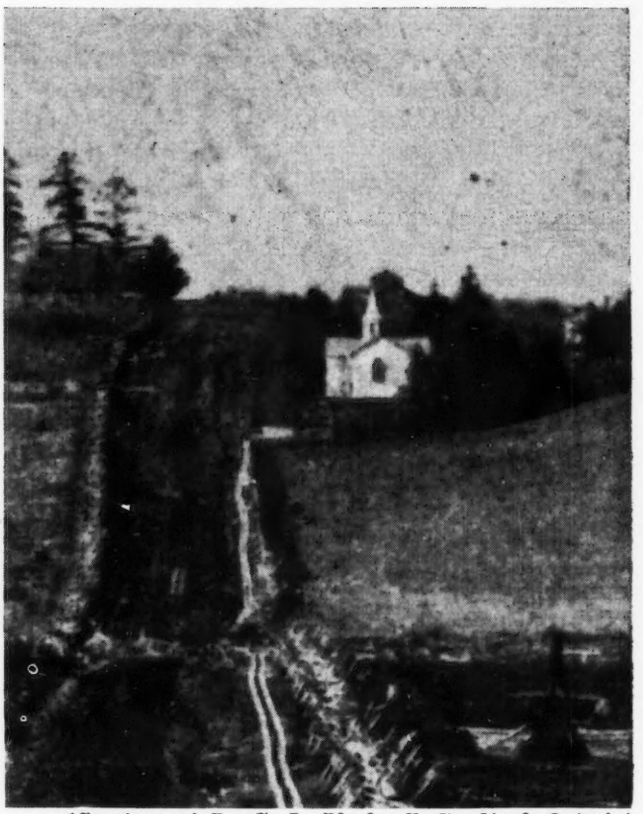
REFERENCE

1. HAWTHORNE, V. M. *et al.*: *Brit. M. J.*, 2: 675, 1957.

MEMORIAL CAIRN TO SIR WILLIAM OSLER

For some years the Medical Historical Club of Toronto has been planning to erect a suitable memorial to Sir William Osler on the actual site of his birth on July 12, 1849.

His father, the Reverend Featherstone Osler, arrived at Bond Head, Ontario (about 35 miles northwest of Toronto), on the Coronation Day of Queen Victoria in 1837. The church, shown in the accompanying photograph, and its adjacent rectory were built for Featherstone Osler approximately one mile west of the village of Bond Head. He was the Rector at Bond Head until 1857, so that William was eight years old when his family moved to Dundas, Ontario. The church was removed the mile to Bond Head village in 1885 and the rectory was later destroyed by fire. Members of the Medical Historical Club have collected stones from the ruin of the rectory, some of which they propose to incorporate in the memorial cairn.



(Courtesy of Dr. G. L. Blackwell, Bradford, Ontario)

This photograph, taken about 1880, shows Rev. Featherstone Osler's church on a rise on the north side of the road from Bond Head to Beeton. The board walk is seen leading from the village to the church (see accompanying text).

The photograph was taken facing west along the road running from Bond Head to Beeton. The Club has had surveyed and is purchasing a plot of ground on the church site, 35′ x 35′, on which the cairn will be placed. The cairn should, therefore, be easily seen by visitors approaching the memorial from Highway No. 27 at Bond Head village and driving west down the Beeton Road. It is hoped that the Province of Ontario, through its Archæological and Historical Sites Board, will provide a sign-post on Highway No. 27 pointing west to the Beeton Road.

The Medical Historical Club is a small organization with a membership limited to 16. It will, therefore, need considerable financial assistance to complete this memorial in a satisfactory manner, as a fitting tribute to that great Canadian, Sir William Osler. The Medical Historical Club of Toronto will be very pleased to receive subscriptions. Cheques should be made payable to the Club and sent to the Secretary, Dr. Eric A. Linell, 253 Blythwood Road, Toronto 12, Ontario.

INTEGRATION OF MEDICAL SERVICES, CANADIAN ARMED FORCES

Until the outbreak of the Second World War, we had only one medical service for our Armed Services, the R.C.A.M.C. Early during the Second World War the R.C.N. and the R.C.A.F. established their own medical services. However, during the last few years serious attempts have been made to exercise greater economy in the utilization of medical manpower by the Armed Forces. This effort has recently culminated in the setting up of a Joint Services Medical Board (J.S.M.B.) with a permanent chairman—the Director General Joint Medical Services (D.G.J.M.S.). Other members are the Directors General of the Navy, Army and Air Force. The complete story is told in a series of articles in the January 1958 issue of the *Medical Services Journal, Canada.* Since so many of our colleagues have close ties with one or another of the Services, they will want to know the principal features of this integration.

This trend was initiated in 1947 when a highly qualified medical adjudicator was asked by the Minister of National Defence to study the problem of amalgamation of the three medical services. This recommendation emphasized the need for a central medical authority to control all functions of the medical service beyond the unit level. This led to the setting up of the Inter-Service Medical Committee, consisting of the Directors General of the three Medical Services and the Director General Dental Services. The committee dealt with all medical problems that had a tri-service aspect and reported directly to the Personnel Members Committee of the Department.

The next step was taken in 1952 and came out of a resolution of the Defence Medical Dental Services Advisory Board (D.M.D.S.A.B.). The Minister of National Defence requested the Chairman of the Board to appoint a sub-committee to inquire into ways and means of closer integration of the common functions of the medical services. As a result the Canadian Forces Medical Council (C.F.M.C.) came into being. This consisted of a civilian chairman—Dr. J. A. MacFarlane, the three Directors General of Medical Services and three civilian part-time members.

This Council charged with the general supervision of the medical services of the Forces had no executive authority. It was considered after three years' experience that further steps were necessary to effect a still closer integration. Consequently in June 1957 and at the direction of the Chairman, Chiefs of Staff, an *ad hoc* committee was appointed to study this problem. Their recommendations were approved and put into effect as of October 1, 1957.

The new Joint Services Medical Board has the responsibility to establish medical policies in relation to all medical activities, subject to the overall control and confirmation by the Personnel Members Committee. The Board is responsible for the professional and medical administrative problems in the operation of National Defence Hospitals and the Medical Joint Training Centre. Another function will be the long-term program for selection, training and employment of clinical specialists, nursing sisters and technical medical personnel of all three services.

The Chairman of the J.S.M.B. will have a small professional staff and all of these positions will be open to members of the three services. The D.G.J.M.S. is the medical adviser to the Chairman, Chiefs of Staff; he is the Coordinator of the C.F.M.C. and as such responsible to the Chairman of the C.F.M.C.; he is the Chairman of the J.S.M.B. and as such responsible to the Chairman of the Personnel Members Committee (other members of J.S.M.B. have the right of approach to their respective Personnel Committee members); he is a member of the C.F.M.C. and of the Defence Research Board Medical Advisory Committee.

The tri-service hospitals, which will commence operation in 1958, will be known as Department of National Defence Hospitals and will be located in Halifax, Ottawa and Kingston. Administration of each of these hospitals will be carried out locally by the appropriate armed force commander, whereas the professional and technical management will come under the purview of the D.G.J.M.S. on behalf of the J.S.M.B. Each hospital will be responsible on a regional basis for the provision of adequate care for all three Armed Forces, and each will be affiliated with the medical faculties of the local university. The medical staff of each hospital will be provided by the three services, selection being based on professional qualification.

The gradual requirement for a more balanced medical service within the Armed Forces has brought with it a more realistic and attractive rank structure in the specialties. This policy was largely developed and strengthened through the efforts of the C.F.M.C. Therefore opportunities for the young well-motivated medical officer who shows a sincere desire to further his professional training will be more varied and better than ever before. Naturally, the specialty chosen must be one for which there is a service need. This is sufficiently comprehensive, however, to offer a satisfactory choice. There are now sixty medical officers in the three services with specialist qualifications either in clinical or aviation medicine, with an additional forty-five holding diplomas in public health, industrial medicine or hospital administration.

The medical profession, I feel certain, will want to join me in complimenting those responsible for this achievement. The Canadian Forces Medical Council had a great deal to do with this, and its membership illustrates the close affiliation that our military medical services have with the medical profession, as follows: Chairman, Dr. J. A. MacFarlane, Dean of the Faculty of Medicine, University of Toronto. Members: Dr. G. E. Hall, President and Vice-Chancellor, University of Western Ontario; Dr. Renaud Lemieux, Medical Director, Hôpital du St-Sacrement, Quebec; Dr. J. Wendell Macleod, Dean of the Faculty of Medicine, University of Saskatchewan. Other members, and also constituting the Joint Services Medical Board, are: Brigadier K. A. Hunter, Director General Joint Medical Services; Surgeon Commodore E. H. Lee, Medical Director General, R.C.N.; Brigadier S. G. U. Shier, Director General of Medical Services, Army; Air Commodore A. A. G. Corbet, Director General of Medical Services, Air.

A. H. NEUFELD

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Medical News in brief

NARCOTIC ADDICTION IN THE U.S.A.

The Report on Narcotic Addiction prepared by the Council on Mental Health, in conjunction with its Committee on Narcotic Addiction of the American Medical Association, has recently been published in the *Journal of the American Medical Association*. The Committee studied the operation of clinics which were set up in 1919 to 1923 in the U.S.A. to dispense drugs to addicts without attempting to rehabilitate them. It finally concluded that it was not feasible at present to recommend re-establishment of such clinics for the supply of drugs to addicts, though this opinion might be subject to review later in the light of new scientific knowledge.

The Committee felt that the incidence of addiction in the United States has declined since passage of the federal narcotic laws, and that there are possibly not more than 60,000 addicts in the U.S.A. at present. Though addiction has increased in persons under 21 years of age, its extent does not justify the degree of public alarm which has arisen. Most such addicts come from minority groups in the slums of certain large cities where the highest rates for delinquency, alcoholism and mental disease are also found. Drug pedlars play a minor role in spreading addiction, which usually spreads from person to person, often as a friendly gesture to a neophyte. Personality disturbances and character disorders are commonly associated with addiction. Opiates do not directly incite to violence, and crimes committed by addicts are usually against property.

Current treatment of addiction is unsatisfactory and the relapse rate high, possibly for lack of facilities for treatment after discharge from an institution.

Among the recommendations of the Committee are the development of institutional care programs in States where the problem is significantly large, study of means to obtain institutional care where the problem is small (possibly several States might set up a joint institution), and development of programs for intensive treatment of addicts after discharge from institutions, including supply of social services, vocational rehabilitation and psychotherapy. At present addicts are committed to institutions mainly through Criminal Courts. Methods should be developed for their commitment by civil action, and the policy of encouraging voluntary admission for treatment of addiction should be extended. It is also recommended that the American Medical Association support any proposals for increased research on the subject, and that it study the narcotic laws to further clarify the rights and duties of physicians in managing addicts.

STAPHYLOCOCCI IN GENERAL PRACTICE

Staphylococcal infection is common in general practice, though data on its epidemiology are scanty in comparison with the wealth of detail obtainable from the hospitals. Drs. Gould and Cruikshank of Edinburgh (*Lancet*, 2: 1157, 1957) carried out an investigation of the epidemiology of staphylococcal infection in an urban general practice. They also report the preliminary results of experiments to prevent recurrence of these infections by suppressing the nasal carriage of staphylococci by local application of antibacterial agents. They find that the proportion of carriers in practice is about 33%. Of the strains isolated 83% were sensitive to penicillin and other antibiotics, and most were of phage types Group I or Group II. It is considered that in such a practice about 5% of total patients have one or more staphylococcal lesions each year; 99% of these are superficial, 67% being boils or septic spots and 19% styes. Nearly all lesions responded to local conservative treatment, and the remainder to systemic penicillin. Of 127 persistent nasal carriers, including 87 with a recent history of recurrent lesions, treatment with local antibacterial nasal cream to suppress nasal staphylococci produced a great decrease in the number of lesions. The creams used contained Hibitane (bis-p-chlorophenyldiguanidohexane) 0.5%, combined with neomycin or bacitracin, or else other antibiotics, according to results of sensitivity tests. It was considered that recurrent staphylococcal infection in nasal carriers may be prevented by applying such a cream to the nose for one week out of four.

RELIEF OF RENAL COLIC

Van Dooren (*J. Urol.*, 78: 727, 1957) describes a simple method for quick relief of pain in renal colic. Usually an area of hyperæsthesia can be located in the flank, running from the costo-vertebral angle down to the groin. The area is mapped out and marked with ink. The skin is cleaned with alcohol and a 5 c.c. syringe filled with 1% solution of procaine. With a No. 24 hypodermic needle, multiple intracutaneous injections of approximately 1/10 c.c. are given, evenly spaced throughout the hypersensitive area. This is claimed to produce instant disappearance of the sharp colicky pain, permitting examination of the patient and radiography.

NEOMYCIN IN TREATMENT OF HEPATIC COMA

It is probable that hepatic coma is often due to absorption of toxic substances from the gut; these substances may be derived from bacterial action of nitrogenous material. For this and other reasons, Dawson and his colleagues from the Post-Graduate Medical School of London (*Lancet*, 2: 1263, 1957) studied the effect of attempts to suppress gastrointestinal bacterial growth by long-term treatment with oral neomycin. They have treated 12 patients in acute hepatic coma and eight with chronic portal-systemic encephalopathy (intermittent stupor) with neomycin for periods of up to 10 months, and observed the clinical state, blood ammonium levels and bacteriology of stools. Of the 20 patients 19 had cirrhosis of the liver and one acute viral hepatitis. The dose of neomycin was four to 10 grams daily. A constant protein diet with vitamin supplements was given throughout in chronic cases. In six patients with a chronic condition, pronounced clinical benefit was seen, associated with fall in blood ammonium level and EEG improvement. The effect on stool flora was variable and not correlated with clinical results. Out of 12 patients in acute hepatic coma seven showed initial improvement but other forms of treatment were used simultaneously.

(Continued on advertising page 62)

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REVIEW ARTICLE

RECENT ADVANCES IN DERMATOLOGIC THERAPY*

A. G. DUNCAN, M.D., *Calgary*

THERE HAVE BEEN MANY advances in the treatment of skin diseases in recent years. The purpose of this paper is to give a brief description of some of these which may be either of use or of interest to the non-dermatologist. An attempt will also be made to evaluate some of the drugs whose virtues are unfortunately not always presented accurately. This is often because of overenthusiasm usually generated by insufficient investigation. The effectiveness of any form of therapy in medicine can only be ascertained after long carefully controlled clinical study.

DERMABRASION

Surgical planing or *dermabrasion*[1-3] has replaced sandpapering because of the better results obtained, and has been used increasingly since 1953. Careful and skilful physicians who shied away from it now recommend it. This does not mean that the results are all near perfect, and that it is without complications. But so far, the results are good and the dangers are few.

Besides acne scars, dermabrasion has been employed with some success in other types of non-hypertrophic scarring, freckles, chloasma, and wrinkles. Results in the port-wine type of birthmarks, tattoos, keloids, and discoid lupus erythematosus have not been altogether satisfactory.[2, 3] This is not meant to imply that it has been completely evaluated; such is definitely not the case.

It is important that the patient have everything about the procedure, including possible complications, explained in full. The type of person who cannot be pleased should not be treated. The scarring should be severe enough to warrant the operation. It is wise to wait possibly a year[3] before the planing, for the passage of time sometimes brings about a startling improvement in bad acne scarring. On the other hand, results are said to be better[2] if the procedure is done early. Therefore the operator has to sum up the pros and cons and decide whether to wait or proceed. Mild active acne is not a contraindication. The so-called ice-pick scars and the undulating type of scarring do not give as good results.

The actual operation is preceded by sedation and preparation of the patient.[2] After cleansing, the skin is frozen with ethyl chloride or one of the newer refrigerants such as dichlorotetrafluoroethane.†[4] The latter freezes more quickly, is non-inflammable, is not a general anæsthetic, and does not require a blower. An area up to two inches (5 cm.) square is frozen, the surrounding skin being protected with gauze. When freezing is complete, the gauze is removed. The planing[1-3] is done with a wire brush (or a serrated steel wheel[5]) attached to a high-speed motor and controlled by a foot-operated variable rheostat. The brush is rotated under gentle pressure with its long axis at right angles to the skin being abraded. The object is to plane the skin down to the level of the scars. This can be seen after freezing. The epidermis and part of the dermis are removed. Further similar areas are then treated until the entire part has been done. No scarring will result if the dermis has not been completely removed. The epidermis regenerates rapidly from the pilosebaceous follicles and the sweat glands.

"Telfa non adherent strip"* is applied[6] after completion and is easily removed without soaking in 24-48 hours. Then, barring complications, the skin is left to heal. At the end of a week the crusts are soaked off with warm water. Careful watch is kept for infection. The patient can usually return to work in about two weeks. Considerable redness is frequently still present, and sunlight must be avoided for at least a month. The only local applications permitted are powder and a cold cream. This procedure can, if necessary, be repeated up to four times at intervals of not less than three months.

Complications[2, 7] include infection, erythema with or without infection, hyperpigmentation, milia, hypertrophic scars, and an eczematous dermatitis which may be severe. Infection is treated with antibiotics. The erythema may be aggravated and prolonged by soap, acne lotions, home remedies, and sunlight. Treatment is to avoid these and to allow only the blandest topical applications. The pigmentation usually fades in a few months. Milia or milium bodies are small cysts in the dermis, and can be removed readily with a sharp needle. Hypertrophic scars may flatten. Injection of a suspension of hydrocortisone may prove to be of value (see below). The vicious, red, moist eczematous dermatitis can be a real treatment problem. The best advice that can be given is not to make it worse. Normal saline or other compresses, mineral oil, or hydrocortisone locally may be used. If these are not effective, systemic administration of corticosteroids may be considered.

The *cutaneous punch* is used by dermatologists for biopsies and sometimes complete removal of small lesions. This may be operated by hand or *power driven*.[8] The latter is done so quickly that it is painless or nearly so, and is particularly useful in children. Whichever method is used, after the specimen has been snipped off with scissors, bleeding can be controlled by means of a *biopsy pressure ring*,† preferably held by an assistant. A piece of

*Presented at the Ninetieth Annual Meeting of the Canadian Medical Association, Edmonton, Alta., June 1957.
†Freoderm—distributed in Canada by Professional Sales Corp., Montreal.

*Manufactured by Bauer & Black, Division of the Kendall Co. It consists of perforated plastic film banded to a highly absorbent cotton fabric.
†Or hæmostasis ring. Robbins Instruments Co., Chatham, N.J.

Gelfoam (Upjohn) cut to fit may be placed in the wound and pressure is then applied followed by a dry dressing. Even with local anæsthesia, this method is quick, the specimen is good, and scarring is minimal. The popular-size punch is 4 or 5 mm., but they range in size from 1 to 12 mm. The smaller are preferred in face lesions. The wound may be sutured, and should be sutured if a larger punch is used.

Another instrument of great value to the dermatologist is his *curette*. The *open type* is preferred, and it must be *sharp*. Often one quick twist of the wrist and the lesion is "off". It is one of the best treatments for warts, including the plantar type, and is an excellent method of removing seborrhœic warts. Also, if desired, a suitable biopsy specimen can usually be obtained. Apart from these common conditions, experience is necessary in picking the type of lesion. It should not be used for nævi (vascular or "moles"). A local anæsthetic may be needed. Electrocoagulation is usually not necessary but if it is, should be done lightly.

Dichlorotetrafluoroethane, the refrigerant mentioned above, may be used for opening furuncles or curetting warts. It only needs to be sprayed on for a few seconds. It apparently does not significantly damage the skin, even if used for more prolonged freezing (as in dermabrasion).[2, 4] It may be employed alone to treat warts, especially in children. A blotter or a strip of gelonet is used with a hole cut in it the size of the lesion to protect the surrounding skin. This is, of course, really a form of psychotherapy; the longer the ceremony, the better the results.

Cryotherapy or freezing of skin lesions and especially warts is quite widely used. Liquid oxygen[9] and liquid nitrogen[10] are colder than carbon dioxide snow, and therefore produce a sharper reaction and possibly somewhat better results.

CORTICOSTEROIDS

The *corticosteroids* have a very definite place in dermatologic therapy. Generally speaking, the response of skin diseases to corticotrophin (ACTH), cortisone, prednisone, etc., is much the same. Side effects do not now seem much less frequent with prednisone and prednisolone. These drugs should, as a rule, be used systemically as a life-saving measure in acute lupus erythematosus (L.E.) and true pemphigus, and occasionally in exfoliative dermatitis. The usual dosages given may have to be greatly increased. In these diseases, cortisone 1000 mg. daily or comparative doses of ACTH or prednisone may be necessary to control the disease initially. It is sometimes advantageous to give ACTH and cortisone together. The usual contraindications may have to be disregarded. When the disease is under control, the dosage is gradually lowered, and a maintenance dose is established. It should be emphasized that the corticosteroids need not be given in every case of pemphigus and acute L.E., and that these diseases do not always respond.

In our old friend *atopic dermatitis*, the corticosteroids should not be employed except in the odd, very severe and stubborn case in adults. The dosage should be kept as low as possible. Frequently, cortisone 25-50 mg. daily or prednisone 5-10 mg. daily as a maintenance dose is sufficient to control the condition and allow the patient to carry on normally.

In severe self-limited dermatoses in which the *cause* or *approximate duration* of the disease is known, a course may be given for a few days, saving the patient much misery and a period of confinement. This applies particularly to contact dermatitis and possibly severe drug and toxic reactions, including urticaria and the more severe forms of erythema multiforme.

In any rapidly spreading dermatitis which cannot be controlled, their use may be justified. This may include contact dermatitis, overtreated dermatoses, autoeczematization from any cause, and cases of vague etiology, some of which may be neurogenic or allergic in origin—or a bit of both.

Corticosteroids should not be used in infants, in pregnancy, in any type of baldness, infections, acne vulgaris, psoriasis, herpes zoster, pityriasis rosea, lichen planus, chronic or subacute lupus erythematosus, or chronic urticaria, to mention a few of the relatively common skin diseases. There may be exceptions, of course, such as herpes zoster with severe pain or widespread uncontrollable psoriasis. In pregnancy it suffices to say that they should be given only as a life-saving measure.

In more or less localized dermatoses, or where only a small amount of skin is involved, the corticosteroids should not be used. There are again exceptions, such as a very severe incapacitating hand eczema resistant to conventional therapy.

If infection is present or appears and corticosteroids are deemed necessary, the appropriate antibiotic is given in adequate dosage. Also, in the above frequently fatal diseases, it is best to use an antibiotic "cover".

It is easy to talk this way and lay down all these rules about these drugs, but we have all been guilty of prescribing the corticosteroids as a way out when the patient is perhaps difficult and not doing well. In the end, however, it usually becomes obvious that it would have been less troublesome to battle it out with conservative remedies. Before instituting treatment, it is frequently prudent to consult the general practitioner of the patient's choice or the appropriate specialist.

Topically, the drug of choice is *hydrocortisone*. Cortisone locally is of no value in skin diseases. According to Goldman[11] prednisone has not as good an anti-inflammatory action on the skin as prednisolone but Frolow[11a] disagrees. These are not as effective as hydrocortisone.[12, 13] The exact mode of action of local hydrocortisone is

not understood. It is anti-inflammatory and antipruritic, but not bactericidal.

It may be used as a lotion* or ointment. The latter are put up in emulsion† and greasy bases.‡ The proprietary preparations are often to be preferred, because of dispensing difficulties.

As a general rule, it should not be used in open, moist skin conditions. I have had patients who could not use the salve or lotion when their dermatitis began and was more or less acute. After this phase, it worked very nicely. Actually the lotion is often more effective in subacute dermatoses, but this varies. In widespread eruptions, the cost is frequently prohibitive, and there is the question of absorption. There has been some evidence of this[14] and the possibility must be kept in mind. It is better then to confine its use to eruptions where skin involvement is not extensive. However, if it controls a hitherto refractory condition, it is certainly preferable to systemic corticosteroids.

Hydrocortisone ointments and lotions have their greatest value in localized dermatoses such as pruritus ani et vulvæ, chronic and recent dermatoses of unknown origin, hand eczemas, atopic dermatitis (infantile eczema) and especially mild cases, some cases of neurodermatitis, eye dermatitis, external otitis, and sometimes in contact dermatitis. It is frequently of value in breaking the scratching habit. This applies to neurodermatitis and other itchy eczema-dermatitis cases. It must, however, be stressed that this drug controls, but cures only by allowing "nature to take its course"; or other methods used in conjunction may produce the "cure".

The effectiveness of the ointment and lotion in chronic conditions varies from patient to patient. A careful history may give information such as intolerance to grease, lotions, and so on, and this may give a lead in prescribing. The lotion may aggravate and the ointment give complete relief in one case, and exactly the opposite may happen in the next patient with the same disease. This, of course, is so true of anything applied to skin lesions. My preference in ointments is usually for greasy bases such as Qualatum,§ Alcolan,¶ or Vaseline, rather than emulsion bases. In the skin conditions mentioned above, it is unusual not to get good relief with one of the ointments or the lotion, and it is not often necessary to switch from one to the other if care is exercised in prescribing.

The strength of the hydrocortisone is important; ½-2½% are the optimum concentrations. Unless one is experienced in its use, a 1% preparation is usually adequate to start with; if this loses its effect, the strength may be increased gradually to 2½%. Many dermatologists use ½% and increase by ½% at a time to 2½% if necessary. Another method is to employ a 2½% preparation until the dermatitis is controlled, and then gradually reduce the percentage of hydrocortisone.

As was to be expected, hydrocortisone has been put up in various combinations with other drugs. That most frequently used is neomycin-hydrocortisone. This sometimes seems to be more effective than hydrocortisone alone in apparently non-infected eczema-dermatitis. The reason for this *may be* that there is a low-grade infection present which is not discernible clinically. It therefore responds better to the antibiotic combination. Hydrocortisone may be of value in lowering the sensitization index of other drugs in these combinations.

9-Alpha-Fluorohydrocortisone (fludrocortisone) used in 0.1% and 0.25% concentrations topically is as effective as or possibly even more so[15] than hydrocortisone, but there have been reports of systemic absorption.[16] If it is applied thinly to localized eruptions two or three times daily, the danger seems to be slight. However, why not use the safer drug?

The treatment of keloids by injection of hydrocortisone acetate[17] shows promise. A suspension containing 25 mg. per c.c. is injected directly into the lesion, preferably with a cartridge-type syringe.[18] The injections should be at intervals of seven to 12 days. Results, as would be expected, are better in recent cases.

ANTIBIOTICS AND SULFONAMIDES

The *antibiotics* and *sulfonamides topically* have been almost exclusively used for skin infections in recent years. *The local use of the sulfonamides and penicillin is to be condemned because of their high index of sensitization.* Also, antibiotics should never be used locally *if* reactions are going to preclude their use later in systemic diseases. Consequently, Terramycin (oxytetracycline), aureomycin (chlortetracycline), tetracycline, and Chloromycetin (chloramphenicol), and any of the more recent antibiotics should not be employed as local applications. There are exceptions, however, such as a severe or refractory pyoderma of the beard. The local antibiotics of choice are definitely bacitracin, neomycin, and polymyxin.

Bacitracin is effective against Gram-positive but not against Gram-negative organisms. It has stood the test of time as far as skin sensitization is concerned. Also it is not generally used systemically.

Neomycin is probably the antibiotic of choice in all staphylococcal infections, but it is less effective than bacitracin against the hæmolytic streptococcus. It is the best topical antibiotic against *Staphylococcus aureus (Micrococcus pyogenes), Staphylococcus hæmolyticus, Staphylococcus albus,* and *Proteus vulgaris.* The lotion* is effective, perhaps even more so than the ointment.

Neomycin, like bacitracin, is not a skin sensitizer. Both of these drugs are excellent for primary or

*Example—1% Hydrocortone Topical Lotion (Merck, Sharpe and Dohme).
†Example—Hydrocortone Acetate Topical Ointment (Merck, Sharpe and Dohme). Base is water soluble.
‡Example—Cortef Acetate Ointment (Upjohn). Base is petrolatum.
§Qualatum contains 93% of a mixture of petrolatum and mineral oil and 7% polyhydric fatty acid esters.
¶Unguentum alcoholium lanæ. B.P.

*Myciguent lotion. Upjohn.

secondary coccal infections, including of course impetigo and folliculitis. I have found neomycin lotion effective as a control in pustular and infected acne.

Another local use for the antibiotics is as a deodorant.[19] Axillary odour is produced by the action of staphylococci and other skin bacteria on the apocrine sweat. Because of its wide spectrum and strong bactericidal action against staphylococci, neomycin (preferably in lotion form) seems to be the best single agent.

There have been reports of monilia *(Candida albicans)* infections following prolonged use of topical neomycin.[20] So far, at any rate, this is a rare complication, but it should be kept in mind.

Polymyxin has the greatest activity against *Pseudomonas aeruginosa.* It is combined with neomycin and bacitracin to give a broad spectrum. In resistant and mixed infections, including those of the ear, this may be indicated.

Nystatin (Mycostatin) seems to be an advance in the treatment of cutaneous moniliasis. It may be used topically as an ointment,* or in a shake lotion.†[21] The latter, as would be expected, seems to be more effective in sweaty regions,[22] and this is where moniliasis is usually found.

Systemically in pustular acne, the triple sulfonamides[23] and broad-spectrum antibiotics[24, 25] have been found of definite value. They may act on bacteria, which are presumably secondary invaders. However, even cases in which the lesions are papular rather than pustular seem to respond. The usual dosage of these drugs is given and this is then decreased to one tablet daily of the sulfonamide and 250 mg. of the antibiotic every day or second day (subtherapeutic doses). This treatment is really a method of control, but may be very useful while possible curative therapy, such as x-ray therapy, is being given. The usual side reactions must be watched for, but are not common with these dosages.

Sulfapyridine controls most cases of dermatitis herpetiformis. It is also of value in some other rare skin diseases.

It is occasionally necessary to use the antibiotics systemically in severe coccal infections, whether these be primary or secondary. Furunculosis is, of course, a problem. In my experience, "boils" originating in hospital respond to erythromycin, chloramphenicol, or best of all, novobiocin, while the etiological agent in outside "boils" is often a staphylococcus sensitive to tetracycline as well as the above.

ANTIHISTAMINES

The *antihistamines* are of value in acute urticaria, sometimes in toxic rashes, and occasionally in chronic urticaria. Also they are useful as antipruritics, but this is probably because of their soporific and sedative effects. In severe cases, one is inclined to fall back on the originals—diphenyhydramine hydrochloride (Benadryl), and tripelennamine (Pyribenzamine). Chlorcyclizine hydrochloride (Perazil) and promethazine hydrochloride (Phenergan) are also useful, but the latter frequently produces drowsiness. These are personal observations; some of the others may be as good as or better than those named. The long-acting drugs seem to be of value, but need further evaluation. In troublesome cases of urticaria, two antihistamines may be given alternately. This is frequently effective and worth trying.

Injection of antihistamines for local anæsthesia[26, 27] requires further evaluation. They could prove very useful with the increasing number of allergic reactions to procaine and related drugs.

Antihistamine lotions or ointments are not recommended. They seem to have some antipruritic action, but their skin sensitizing properties are such that they should not be used.

For want of a better place to damn drugs for local use, let us here add the -caine drugs. Our list now includes topical sulfonamides, penicillin, antihistamines and the drugs related to procaine.

OTHER DRUGS

The antimalarial preparations have replaced bismuth and gold in the treatment of *chronic* (or discoid) *lupus erythematosus.* Their mode of action is not known. They do, however, lessen sensitivity to sunlight (photosensitivity). Lupus erythematosus frequently follows or is aggravated by overexposure to the sun.

Atabrine (quinacrine or mepacrine) was the first of these to be used. It produces a yellow discoloration of the skin and has several severe side effects including bone marrow depression, hepatitis, and chronic skin lesions.

Chloroquine diphosphate (Aralen) has replaced Atabrine and is now generally used. Dosage is 250 mg. twice daily for a week or two, then once a day for possibly three weeks, and then every second day. In many cases it must be taken for prolonged periods to control chronic L.E. The reactions I have seen from this drug have been headache, nausea and vomiting, photophobia,* greying of the hair, and a moderately severe urticaria.

Camoquin[28] (amodiaquin) shows promise in discoid L.E. The dosage is 200 mg. b.i.d. for one week, then 200 mg. daily. It requires further evaluation. *Plaquenil*[29, 30] (a 4-aminoquinoline) is another antimalarial drug being investigated.

The antimalarial drugs also are of definite value in eruptions due to *photosensitivity.* The dosage is the same as for chronic lupus erythematosus, with *chloroquine at present* the drug of choice. However, they must be taken as long as the patient is exposed to the sun. A dosage of chloroquine as

*Squibb's—500,000 units Mycostatin per g. plastibase.
†Mycostatin tablets 500,000 units; three tablets crushed are added to two ounces of calamine or zinc lotion.

*Patient examined by Dr. J. F. Aikenhead. There were no abnormal eye findings.

low as 125 mg. every second day may be sufficient to allow outdoor workers to carry on with their occupations in the summer. These drugs may also be of value in confirming the diagnosis of photosensitivity. Just how they protect from the sun is not known. They are of no use as a sunburn preventive in those with normal skins.[31]

Isoniazid (isonicotinic acid hydrazide) is the drug of choice[32] in cutaneous tuberculosis. Results have been excellent. It has replaced vitamin D_2 (calciferol) and para-aminosalicylic acid. It may be used in combination with streptomycin, but it is probably preferable to give them separately.

Now what is true of all these new (and not so new) highly advertised remedies? Let us call them "the high pressure drugs".

There have been many new *tranquillizing drugs* in very recent years. Their value in dermatology has been subject to conflicting reports.

The *rauwolfia derivatives* have been reported as being of considerable value in skin diseases in which there are psychogenic factors.[33] In my own experience they are of no great value and side effects are too frequent. These include drowsiness, gain in weight, nasal congestion, diarrhœa, skin eruptions and mental changes including severe depression.[34]

Chlorpromazine (Largactil) seems to be of value in such skin conditions as pruritus ani et vulvæ, atopic dermatitis, and various neurodermatoses. In a limited number of cases of my own, small doses seemed effective. However, jaundice, convulsions, and bone marrow depression have been reported, as well as sensitization to sunlight. Therefore the risk seems too great except possibly in very severe skin cases.

Meprobamate (Miltown, Equanil) seems to be a useful quietening drug. My impression is that it is of value in some agitated patients. Side effects seem to be increasing and include muscle spasms, drowsiness, nausea, headaches, dizziness and skin eruptions. This drug shows promise, but still needs further evaluation.

The various ringworm remedies include Desenex (undecylenic acid-zinc undecylenate), Sopronol (propionate and caprylates), Asterol (dimethylamino-6-(β-diethylaminoethoxy)-benzothiazole dihydrochloride) and Salundek (salicylanilides-undecylenic acid-zinc undecylenate), with more coming. These are of value as fungicides, but are generally regarded as being inferior to the older topical remedies, viz. Whitfield's ointment,* ½-1% gentian violet (methylrosaniline chloride), Castellani's paint,† and so forth.

Silicone ointments as protectives have been very disappointing, and are certainly of no great value.

Acid mantle cream. In housewives, cement workers, and those exposed to petroleum products, the acid mantle of the skin is destroyed. The skin becomes alkaline, loses its power to neutralize alkalis, and is subject to irritations and infections. This cream is supposed to restore the protective acid mantle. While the theory is of interest and is being given further study, this does not appear to be the answer.

Vioform (iodochlorhydroxyquinoline) ointment and cream and Sterosan (5, 7, dichloro-8-hydroxyquinaldine) ointment and cream are similar in action as well as being chemically related. They have an antifungal and antibacterial effect on the skin. They are therefore useful in infected ringworm or eczemas. Their index of sensitization seems, however, rather high. Combined with hydrocortisone they show definite promise.

Eurax cream (n-ethyl-o-crotonotoluide) seems to be a good antipruritic and is also an excellent scabicide. It stings if the skin is abraded, and its sensitization index may be somewhat high.

Benzoped (contains 10% benzyl benzoate, 1% D.D.T. and 2% benzocaine in an emulsion base) is excellent in scabies and lice.

Metanium (salts of titanium) is available as an ointment or powder. It is reported[35, 36] to be soothing and to rival hydrocortisone in effectiveness. My experience, while limited, has not confirmed this.

Pragmatar (tar, sulphur, salicylic acid) is an excellent preparation for seborrhœic dermatitis. It is water-soluble and pleasant, as scalp ointments go. It should not be employed in acute cases.

Selsun (selenium sulphide) is definitely useful for seborrhœa sicca, especially as it is so easy to use. However, as it tends to increase the oiliness of the scalp, it is of no value in oily seborrhœa, as found in adolescents.

Hexachlorophene is an excellent bactericide, is useful as a skin cleanser, and is a very effective deodorant.

Vitamins. Vitamin A seems to be of value in acne vulgaris when there are a large number of comedones present. Vitamin B complex may help rosacea. Phosphorylated riboflavin by intramuscular injection is being investigated in psoriasis.[37]

Œstrogens in acne.—If the condition tends to flare-up around the menses, this frequently is useful as a control. Topically it has probably no value.

Vaccines and toxoids in acne and furunculosis. Every dermatologist has seen the occasional good result. The best explanation is that the injections were given when the disease was undergoing spontaneous remission.

The anticholinergic compounds (Banthine, Pro-Banthine, Prantal) diminish sweating, and are useful in hyperhidrosis and dermatoses caused or aggravated by sweating. Prantal cream seems to have no effect on excessive sweating or, for that matter, any dermatological virtue.

Gelatin[38] taken in dosage of 7 g. daily seems to be of value in some cases of soft or brittle nails of unknown etiology. In my experience, it is useless in psoriasis of the nails.

*Salicylic and benzoic acids.
†Carbol fuchsin, boric acid, acetone, resorcinol, and phenol.

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Protamide (proteolytic enzymes) is of no proven benefit in herpes zoster.

Calcium gluconate intravenously has probably no definite value except as a rather good psychotherapeutic agent. The type of patient who wants and demands active therapy thinks he is really getting "hot" treatment.

Piromen (a Pseudomonas polysaccharide) has in itself probably no therapeutic value.

8-Methoxypsoralen has received much publicity as a pigment producer and protective in persons sensitive to sunlight. This, however, is not factual as the drug "augments all cutaneous responses to solar radiation".[39] Its use in vitiligo has not been satisfactory as the re-pigmentation is seldom complete and rarely if ever permanent. Also, severe local and systemic reactions occur.

SUMMARY

A brief description of some of the newer dermatologic surgical procedures has been given, and the value or otherwise of some of the more recent drugs has been mentioned. Then, in a few words, an attempt has been made to separate the "wheat from the chaff" in a few of the much publicized and highly advertised remedies.

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GENERAL PRACTICE

THE USE AND ABUSE OF THE TRANQUILLIZERS*

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BEFORE DISCUSSING the use and abuse of the tranquillizing drugs, we should briefly consider their nature. For a long time efforts have been made to develop drugs which will suppress the manifestations of psychosis and neurosis without disabling sedation. Rauwolfia and its alkaloids gained wide clinical acceptance early in this decade because of their hypotensive properties, but since then have been employed widely as tranquilizers.

HISTORY

In 1952 French workers produced the phenothiazine derivative chlorpromazine, better known by its proprietory name, Largactil. Enthusiastic reports of its effectiveness stimulated chemists to search for other substances with similar or superior properties. Since then many preparations have been made commercially available, all purporting to have basically the same action of soothing rather than sedating. Structurally most of these are variations of phenothiazine and closely related to chlorpromazine. They are familiar to clinicians as Sparine, Phenergan, Diparcol, Pacatal, and Trilafon. Others are entirely unrelated, such as meprobamate (Miltown and Equanil), hydroxyzine (Atarax), captodiamin (Suvren), azacyclonol (Frenquel), benactyzine (Suavitil), and several others.

Together they have been grouped as the ataractic drugs, a name derived from the Greek *ataraktos*, meaning "freedom from confusion, and peace of mind".

Despite their diversity of structure, the ataractics appear to have a similar mode of action. A considerable body of physiological work suggests that, although they act on all the cells of the central nervous system, certainly including the cortex, a principal action is subcortical. They are believed to affect the reticular substances of the brain stem and mid-brain, suppressing several centres of autonomic activity. Independent observers agree that the ataractics have an important if not a preponderant hypnotic action. This view is not shared by the proprietors of the different ataractic preparations, some of whom deny sedative action altogether, while others claim it as an added therapeutic virtue.

PRESENT REVIEW

The present review of the recent literature on the tranquillizers has been confined to abstracting the material from about 20 of the leading English-language journals, those of such acknowledged prestige that the editors can usually select what they want to print. Even in these, papers appeared which would not stand up to reasonable critical

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appraisal. It was therefore not considered profitable to explore the scores of peripheral publications, many of which appear to exist for the benevolent purpose of soothing *pruritus publicendi*, or of accommodating those who must publish to keep their jobs.

A summary of clinical experience with the ataractic drugs will be discussed under the headings of psychosis, psychoneurosis, anxiety states, alcoholism and anæsthesia.

THERAPY OF PSYCHOSES

In the process of searching the literature, a totally unexpected fact emerges. Most of the articles about the tranquillizers in the general journals are written by psychiatrists about chronic psychotics, under institutional care and being given relatively huge doses of the new drugs. Also impressive is the good agreement of their findings.

Most of the observations reported so far have been on reserpine and chlorpromazine, because these have been available for study the longest. Most of these studies appear to meet a high standard of competence and objectivity. Almost invariably the double-blind technique was used—that is, neither the patients nor their doctors knew which was getting treatment and which a placebo. Under institutional conditions, patients could be continuously observed by experienced personnel. Evidence of improvement was assessed by different psychiatrists, generally according to a complex scoring system, reducing subjective evidence to a minimum.

There is almost uniform agreement as to the response of different psychotic states to the ataractics. Patients with acute or recently developed psychoses do better than the chronically regressed. Paranoid or catatonic schizophrenics and manic patients are the most responsive subjects. The results with hebephrenics have been uniformly poor.

Observers are almost unanimous that the best results are obtained where agitation and tension are severe. Hostility, restlessness and aggressiveness often respond well. Incontinence is reduced. Patients are more tractable, more approachable, more orderly. That they are less destructive is noted so regularly that it seems as if one more statistical article should be written, balancing the cost of the tranquillizers against the saving in furniture not smashed. Intrinsic psychotic mechanisms, however, remain unaltered. Delusions and hallucinations are unaffected; at best patients become indifferent to them.

There is a considerable spread among different series of cases as to the proportion of patients showing moderate to marked improvement. As a fair average, about two-thirds are substantially helped. That all this improvement cannot be credited to the tranquillizing drug is suggested by the fact that equally good results are noted in one-quarter to one-third of control groups on placebos. This is not surprising if one thinks of the almost intolerable drabness of the life of a chronic psychotic in our overcrowded and understaffed mental institutions. The frequent administration of a pill and the periodic talks with the appraising doctor represent in themselves a therapeutic dose of attention and solicitude.

There is a minority report from a private mental hospital where a staff outnumbering the patients provided an expensive, intensive schedule of psychotherapy, occupational therapy and physiotherapy, and entertainment. It was considered that of 100 patients to whose treatment a high dose of chlorpromazine or reserpine was added, in only 20 did the resultant sedative action contribute ponderably to their treatment.

But for the vast majority of the mentally ill, for whom such de luxe care is not available, the tranquillizers appear to offer at least a valuable degree of tranquillity to the patients and peace to their attendants.

Beyond that, in the range of real remission, a much more modest success has been noted. Eleven thousand and eighty schizophrenics were reviewed by Freeman with respect to their rates of "social recovery" with different kinds of treatment. On custodial care, 19% spontaneously got better and went home. For electroconvulsive therapy the figure was 29%, for insulin coma 48%, for chlorpromazine 34%, and for reserpine 22%.

The drugs seem specially useful among senile psychotics. When they are agitated, confused, restless and irritable, up to 75% benefit from the ataractics to such a degree that many hospital patients can be sent home on maintenance doses. It should be noted here that all workers agree that, where these drugs have induced good remission, if they are withdrawn the relapse rate approaches 100%.

However, for only chlorpromazine and reserpine has there accumulated a body of independent expert opinion large enough for comparative evaluation to be fair. Experience with reserpine has been based on a daily dosage varying from 2 to 15 mg., and with chlorpromazine from 400 to 2000 mg. There is no general agreement as to the relative merits of these two. Opinions range from that of Penman and Dredge, who found reserpine no better than placebo, to that of Zeller, who rated the two drugs as equally effective. In general the question seems to have resolved itself into whether reserpine is as good as chlorpromazine or not. In one survey of 22 psychiatrists with wide experience, 19 preferred chlorpromazine.

THERAPY OF PSYCHONEUROSES

Psychoneurotics are identified in this discussion as individuals apart from the social norm. Their emotional disturbances are severe enough to prevent their meeting the obligations of their environment or they do so in precarious adjustment. As members of the community they are generally ineffective. These people are sick and need treatment. How valuable are the tranquillizers in treating them? According to the current literature, the answer is far from clear. Compared with the work on psychosis, there are surprisingly few reports. Series of cases are much fewer; patients are studied in dozens rather than in hundreds. Many of these are difficult to assess because they stem from private practice where the physician's prime obligation is to his patient and not to scientific objectivity, and psychotherapy was therefore given

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at the same time as the tranquillizers. Most studies have had to be made on out-patients, so that observation is limited, and assessment becomes largely based on the doctor's interpretation of the patient's statements. Conclusions may be coloured by bias. Enthusiasm can lead to incredible naïveté. One man, reporting in an august national journal, said that a certain tranquillizer was so effective that not only did all of his 15 neurotic patients get better on it, but eight of them (53.3%) even maintained their improvement subsequently on placebo. He gravely cites this as "an instance of the therapeutic prolongation pattern". Another man, after reporting that a different tranquillizer induced marked improvement in 65% of his patients, added grandly that more would have done well had it not been for "their neurotic need to remain sick".

At the other end of the scale, Sargant, who reports favourably on his work with psychotics, thinks that in the neuroses the ataractics' disadvantages outweigh their advantages. He states that bromides and barbiturates, fallen from grace because of over-use, should be reinstated. He adds that chlorpromazine is a valuable drug; if one wants to potentiate the sedative action of phenobarbitone, it is every bit as good as bromide.

Majority opinion, or such of it as has thus far been published, predictably occupies a middle ground. One is able to form a fair synthesis of opinion on the following points:

In favourable comment on the effect of the ataractics on neurotics the three words most often recurring are *agitation, anxiety* and *tension.* Where these are prominent the new drugs seem often effective in giving the patient symptomatic relief, and thus making him more amenable to psychotherapy. There is no effect on the ideational content of the neuroses. Some patients explain that their problems create less tension; others that they can deal more realistically with their problems; others that they achieve a sense of divorce between outer reality and emotional reactions. The tranquillizers thus appear able to calm seriously disturbed neurotics to a point where they can live with their neuroses.

Whether they do it better than barbiturates remains controversial. In one of the few double-blind studies, West and da Fonseca noted that among 51 psychoneurotics 10 were more improved on phenobarbitone than on meprobamate, nine were more improved on meprobamate than on phenobarbitone, nine were about equal, four improved only on phenobarbitone, three improved only on meprobamate, and 16 showed no benefit from either.

There are favourable reports on the effect of the tranquillizers in hypomanic states and sometimes in obsessive-compulsive neuroses. There is general agreement that they are ineffective in conversion hysteria and definitely contraindicated in the depressions. Most reports on a series of cases record marked to moderate improvement in a proportion of patients ranging from one-half to two-thirds. In one of the few large studies, on 644 consecutive patients at the psychiatric out-patient department of Westminster Hospital, the short-acting barbiturates were considered the drug of choice, but in a few cases the patients did better if this was supplemented with a small dose of chlorpromazine.

Among the individual drugs, most authors feel that chlorpromazine produces sedation without clouding of the intellect more selectively than the other drugs. Benactyzine, still much less widely studied, may share this property. Meprobamate has a marked sedative action, but is also notable as a muscle-relaxant in severe tension. An increasing number of workers are stating that, because of its depressant effect, reserpine should not be considered among the tranquillizers in treatment of the neuroses.

Despite widespread claims to the contrary, independent observers agree that patients do become habituated to the ataractics, and do experience withdrawal symptoms from them. Judgment and efficiency are in some degree impaired under their influence, sometimes severely, and when a patient contends that he is just as alert as without medication, he is only demonstrating that euphoria has made him uncritical of his performance. For these reasons, men with the widest experience in the use of these drugs emphasize that they are not indicated in chronic treatment, but that their use should be reserved for limited periods during acute phases of neurosis, when the patient is under close observation, preferably combined with active psychotherapy. And it is worth emphasizing that the best results are all reported with the constant repetition of the words *agitation, anxiety* and *tension.*

TENSION STATES

Fortunately the disabling psychoneurosis afflicts only a small part of our population. But lesser anxiety and tension states, in response to the stresses of environment, affect a high proportion of it, including its full share of at least one learned profession. These people are not sick and they are not community liabilities. On the contrary, tension states, often accompanied by somatic disturbances, are a frequent by-product of success in our competitive society. Yet it is among millions of basically well-adjusted people, anxious over normal worries, tense in meeting normal difficulties, agitated by the insecurities of an uncertain world, that the tranquillizing drugs have found their most enthusiastic acceptance.

In the United States last year an estimated 50 million prescriptions were written for the tranquillizers. At any one time 5% of the population was under medication with them. In the first nine months of that year, one manufacturer of a popular tranquillizer sold 30 *billion* tablets. In New York 10% of all prescriptions written were for tranquillizers. In Canada the position, if not as fantastic, must be at least comparable. The lay press teems with articles giving the impression that the elixir of happiness has been found; the doctors' desks are covered with brochures expensively indicating in carefully scientific jargon that the door of the corner drugstore is the gateway to Nirvana. The eager and gullible public puts its physicians under pressure to supply happiness pills, while the latter all too often succumb to the discovery that here is an effective agent for getting the patient out of the office and the doctor out on the golf

course. At some levels the ataractics have become not a new instrument in the practice of medicine, but successors to the vitamins as a facile substitute for it.

With all this fanfare one would think that our professional literature would be full of studies of the tranquillizers in minor stress states, but when one turns from the fanfare to the literature, it is like stepping from a football stadium into a Quaker meeting. One learns with amazement that the enormous popularity of these drugs is unsupported by any weight of independent professional opinion at all. Apart from an occasional article condemning their frivolous use, there is silence.

There is no good evidence that, in mild dosage for mild disorders, the tranquillizers have any beneficial action other than to relax and sedate. To millions of people who have to be a bit numb to stand their own company, this is enough. But far beyond this, the tranquillizers have been thrust on a troubled world as pills with unique properties which will make anxious, worried people into happy, peaceful people. This appeals to the very foundation of conviction, which is the will to believe. Doctors with genuine enthusiam are prescribing these drugs to patients who are determined to be transformed by them. What they have to pay for their prescriptions does not diminish their awe. The emotional bandwagon rolls on at an evangelical pace, and the tranquillizers are still being credited with inducing a serenity which heretofore has been achieved only through the consolations of philosophy. As one psychiatrist says, "Let's use these drugs all we can while they are still effective."

No final assessment of the value of the tranquillizers in treating minor tension and anxiety states can be made in the current tent-meeting atmosphere. When this is eventually possible, it may be concluded that in mankind's naive but age-old search to get happiness out of a bottle, the tranquillizers will rate as being a good deal more expensive than phenobarbitone and a good deal less honest than whisky.

OTHER USES

This brings us logically to the use of the ataractics in acute alcoholism, and returns us to studies of large numbers of cases, objective reporting, considerable agreement and a welcome sanity. The authors of several articles, describing their findings in series of cases up to 750, are all impressed with their uniformly satisfactory results.

The specific anti-emetic effect was found to be so reliable that, after an initial injection of the ataractic, the drug could be given by mouth. Symptoms of gastritis disappeared in a few hours. Nearly all patients got relief from the shakes. Insomnia was not troublesome. During the first days of withdrawal none got delirium tremens. Direct comparison with barbiturates was made only in one study, where meprobamate was considered superior. There was some difference of opinion as to the relative merits of chlorpromazine, promazine and meprobamate. Doses were larger than conventional, with a tendency to postural hypotension in those taking chlorpromazine.

Similar results have not been obtained during withdrawal of narcotics from addicts. Neither chlorpromazine nor reserpine has been found to reduce the intensity of withdrawal symptoms, while chlorpromazine prolongs the period of morphine euphoria to about double the usual time.

The widespread acceptance of the phenothiazine drugs, particularly promethazine, as an adjunct in anæsthesia is based on favourable reports of their use in series totalling many thousands of cases. Given 1½ to two hours preoperatively they allay apprehension and substantially reduce the amount of anæsthetic required. Often in major surgery only small amounts of nitrous oxide and intravenous Demerol are needed in supplement.

There is a considerable body of opinion that operative shock is reduced. One experienced observer states that hæmorrhagic shock can be reversed by replacement of only one-third to one-half of the blood loss under cover of 50 mg. each of chlorpromazine and promethazine. Muscle tone is reduced at operation, as is the irritability of the peritoneal and respiratory reflexes.

Suppression of autonomic activity is believed to provide a smoother postoperative course with minimum recourse to opiates.

Some authors state that hypotension and tachycardia are inconsiderable and transient. Others insist that the hypotensive action is very unpredictable and often profound; after a few alarming experiences they have returned to the older agents which they feel are easier to control.

Although they have not gained universal acceptance, it would appear that the ataractics have found an established place in anæsthesia.

SIDE EFFECTS

Most new drugs share a common experience in their reception by investigators. First comes the enthusiastic volley about their main action, shortly followed by rather gleeful sniping at their side-effects. The ataractics are no exception. The 1957 literature contains more articles about their toxic vices than their therapeutic virtues. These are admittedly numerous. Some are unique to one of the drugs, others common to most of them.

It has been noted that they have an important influence on the autonomic centres of the mid-brain and brain stem. Here is logical basis for the incidence, depending on how the autonomic balance is swayed, of postural hypotension, hypothermia, diarrhœa, tachycardia, blurred vision or mucosal congestion. The cerebral cortex is significantly affected, with a response varying from mild hypnosis in the many to stupor in the few. Nightmares and bizarre behaviour have been reported. There has been a substantial incidence of severe depression in patients taking reserpine, with some suicides. Convulsive seizures have attended the use of the phenothiazine drugs. Patients on meprobamate have experienced paradoxical excitement of almost maniacal intensity. Extrapyramidal pathways are frequently affected, and many writers describe a state clinically indistinguishable from Parkinsonism. Under pecazine therapy there have been instances of unilateral hypotonia amounting almost to hemiplegia.

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Outside the central nervous system, reserpine has been shown to increase gastric acidity. Quiescent peptic ulcers may be activated, and massive hæmorrhage has occurred. Agranulocytosis is uncommon, but one review now over a year old cites 22 cases, eight of them fatal, in chlorpromazine-treated patients.

Although troublesome side effects are very common, most of the serious ones are reported by the psychiatrists in the course of treating psychotics, where the doses used are several times those recommended in ordinary practice. There is little doubt that their incidence is related to these high doses.

Two noxious effects of the ataractics are seen quite often in general practice. The commoner is jaundice induced by the phenothiazine drugs. On conservative dosage, the incidence is reported as about 1.4%. This is obstructive in character, and is due to periportal infiltration with round cells, chiefly eosinophil, with biliary stasis. The condition invariably clears within a few weeks of withdrawal of the drug. Mild pre-existing liver damage does not appear to predispose to this condition.

Meprobamate can cause a transient morbilliform skin eruption and sometimes a prolonged erythema multiforme. But far commoner is a contact dermatitis due to chlorpromazine. This is not restricted to contact areas, but affects all light-exposed surfaces. Several reports indicate that it has become a considerable nuisance among nurses handling the drug. The eruption clears on withdrawal of contact.

Not related to direct drug toxicity, but of great importance in using the tranquillizers, is the fact that they have a very marked action in potentiating the barbiturates and alcohol. Used without due caution in conjunction with the former, in patients under aggressive hospital treatment, the result can be lethal. Used carelessly with the latter, by patients who drive cars, they can be equally so.

Drawing attention to the dangers of new drugs is necessary, but beyond a certain point they can be emphasized too much. All therapy is a calculated risk, and people have died from taking an aspirin. It is becoming more so as we develop more potent drugs. With so many of our new therapeutic weapons, the more dynamic the action, the more dramatic the side action. As Donald Hunter use to tell his students: "Gentlemen, never forget that the age of dangerous surgery is drawing to a close, but the age of dangerous medicine is just beginning." The ataractics not uncommonly induce side effects which are often distressing, sometimes dangerous. But this is no more reason to discredit their use, on correct indication and under close supervision, than to abandon cortisone, chloramphenicol, the antithyroid drugs or digitalis. Their dangers should, however, stand as a barrier to their indiscriminate use, under loose control, when the therapeutic risk becomes unreasonable.

ANXIETY AND TENSION

As has been indicated, apart from the lay press there is almost no independent opinion about the value of, or indications for, the tranquillizers in those mild-to-moderate states of anxiety and tension for which they have achieved such an enormous popular reputation. The practising doctor's chief source of information is the torrent of artfully designed, carefully written brochures with which the manufacturing chemists advertise their competitive wares. Hence the question whether these wares are being fairly described becomes important.

Recently at the request of the Commissioner of Health of New York, the New York Academy of Medicine appointed a committee on public health to investigate the promotion and sale of the tranquillizers. This committee reported that the advertising: (1) gives frivolous indications for the use of the drugs; (2) does not adequately stress the hazards of prolonged use; and (3) uses "expensive, extravagant and indiscriminate listing of indications with inadequate citation of side reactions".

Particularly disturbing are the states for which we are urged to prescribe these expensive and sometimes dangerous drugs. Indications are listed of symptoms so numerous and so common that almost every one alive must suffer from several of them. They include homesickness or restlessness in children, fear, fatigue, pruritus, working in a noisy place, having differences of opinion, and going to weddings. This brings up, in conclusion, an important philosophical consideration.

The tranquillizers may be useful in treating anxiety and tension which are severe enough to make the individual ineffective. But their phenomenal demand arises chiefly from a desire of millions to suppress the stresses and strains of everyday life, to blunt themselves against the pin-pricks of environment, to make them indifferent to their problems. A proud claim for one drug was made that normal subjects reported that it so relieved their "hostilities" that they couldn't even start an argument.

In areas of the world where living consists in toiling at a subsistence level, with no hope of a better future, whole populations blunt their misery with coco leaves or hashish. Are we in a position to pity them, while apparently trying to sedate and relax ourselves into a generation of ciphers?

Anxiety and tension are inherent in the solution of problems, and solving our problems is a continuing process in the development of an individual or a society towards maturity. Escape into indifference is decadence. Our civilization has been built on the divine discontent of tense men. Had they not in every generation become anxious over problems, we might still be ploughing with pointed sticks. Perhaps Columbus could have discovered the New World while taking tranquillizers, and Beethoven might have been able to compose his symphonies, but I submit that if they had been full of meprobamate they wouldn't have bothered.

612 View Street.

HOUSING APPLICATION FORM

Halifax, June 16 - 20, 1958 — 91st Annual Meeting, C.M.A.

Dr. M. R. Macdonald,
Chairman, Committee on Housing, C.M.A.
30 Armshore Drive,
Armdale, Halifax, N.S.

Please reserve the following accommodation:

..... Double room (bath or shower) twin beds ..... double bed.....

..... Room for ..... person(s) (bath or shower)

..... Motel Unit for ..... persons (bath or shower)

..... Tourist Home for ..... persons

In view of the large attendance expected, the hotels have few, if any, single rooms available. It might be to your advantage to share a room with another member. Please mention below the name of the person with whom you would like to share your accommodation; otherwise assignment will be made by the Housing Committee.

Names of persons who will occupy the accommodation requested above:

NAMES (Dr. and Mrs.) ....

ADDRESSES ....

I (we) will arrive in Halifax on June..... at ..... a.m. p.m.

I (we) will depart from Halifax on June ..... at ..... a.m. p.m.

Travelling by: Automobile..... Train..... Air..... Bus.....

Please check choice of accommodation:	First	Second	Third
Hotel	.....	.....	.....
Motel	.....	.....	.....
Tourist Home	.....	.....	.....

NAME .....

ADDRESS .....

.....

TELEPHONE No.....

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Association Notes

THE 91st ANNUAL MEETING

Our annual meeting this year will be held in Halifax, Nova Scotia, on June 16-20. As usual, we will run a series of notes on the neighbourhood for the benefit of visitors. Since the host society is technically the New Brunswick division and the President-elect a New Brunswick man, it is fitting to begin with a story on Fredericton, New Brunswick, a very visit-worthy city. The other Atlantic provinces also have a share in the meeting, and future issues will contain something about them. The story below comes to us by the courtesy of the New Brunswick Tourist Bureau (Director: Mr. R. A. Tweedie).

FREDERICTON

Fredericton, New Brunswick—birthplace of Dr. Arthur F. VanWart, incoming President of the Canadian Medical Association—while steeped in glorious tradition is bubbling over with enthusiasm for the arts and sciences and may well become the leading centre of culture along the eastern Atlantic seaboard.

And while this attitude has been evident in some degree in Fredericton from the day it became a city in 1848, it has been through the generosity of an "outsider" that the capital city has reached its present status and will move forward to a place of respect in the world of culture.

The "outsider" is Lord Beaverbrook—freeman of the City of Fredericton, whose latest gift to Fredericton in particular and the province in general is the Beaverbrook Art Gallery slated to be officially opened in September 1958. Some of the world's most famous paintings will be housed here, giving resident and visitor the opportunity of viewing works of the great masters and also contemporary pieces included in travelling exhibitions.

The University of New Brunswick, on a hill overlooking the City of Fredericton and one of the continent's most famous seats of learning, benefits from the keen interest of its lifetime honorary chancellor, Lord Beaverbrook. Leaders in many fields of endeavour are serving mankind and enjoying the benefits of opportunities made possible through scholarships and special funds established by him.

The colourful old arts building in the centre of the campus, completed in 1828, is the oldest college building still in use in Canada. It houses offices of the administration, in addition to its classrooms and faculty offices. The initials of the university's pioneer students can be found carved in the antique desks and benches of one of the classrooms.

There are many other interesting buildings on the campus, among them the famous old observatory built in 1851, the first structure in Canada to be used for that purpose. In contrast to the very old buildings, the university boasts several new and modern structures including the new Memorial Students Centre and the Bonar Law-Bennett Library given by Lord Beaverbrook. This library houses many priceless historical and literary treasures from his personal collection.

Another source of pride to the capital is the province's majestic Legislative Building erected in 1880. The Legislative Library, housed in an annex at the rear, has a copy of the original Domesday Book (1087) printed in 1783, one of the two sets of the Audubon bird paintings in existence, and a set of Hogarth prints made from the original steel engravings.

Sequestered amid tall elm trees in a commanding spot in the city where loving hands of a century ago laid its corner stone, Christ Church Cathedral is one of the outstanding examples of religious architecture on the North American continent. The laying of the corner stone 112 years ago was in itself an event unique in ecclesiastical history, for it marked the erection of the first new cathedral foundation on British soil beyond the shores of England since the Norman Conquest in 1066. The edifice was completed and consecrated in 1853.

However hallowed the cathedral may have been, it was not invulnerable to a bolt of lightning which struck its spire and tower in 1910 and destroyed an admirable chime of eight bells in the tower. This probably was a blessing in disguise, for on August 31, 1913, another chime of 15 bells, adapted from that of Trinity Church in New York, was presented to the cathedral by the late Sir James Dunn in memory of his grandmother, Mrs. James Dunn of Bathurst, New Brunswick. Priceless ecclesiastical cloths and hangings are part of the Cathedral's treasure.

NEW ARRANGEMENT WITH D.V.A.

For approximately two years negotiations have been proceeding with the Department of Veterans Affairs, with a view to instituting provincial fee schedules as the basis for payment to physicians rendering service to entitled veterans under the doctor-of-choice plan. On three occasions the Treasury Board has ruled that D.V.A. may adopt provincial schedules, but that payments to physicians be made on the basis of 90% of the appropriate official schedule of fees.

The most recent investigations of the Advisory Committee to the Federal Government have led to the conclusion that a more favourable outcome is unlikely to be reached, and the position was reported to the Executive Committee in the form of a mail ballot. The vote of the Executive Committee has authorized the acceptance, under protest, of the offer of payment on the basis of 90% of provincial schedules and we have so notified the Minister of Veterans Affairs, expressing our hope that experience with the operation of the plan will be so favourable that the discount will no longer be applied.

We are now advised by Dr. J. N. Crawford, Director General of Treatment Services, that the new basis of payment will be instituted, effective January 1, 1958. The following significant section is extracted from the D.V.A. directive, issued on December 10, 1957, to all districts of the Department:

> "The Department shall pay for medical services provided from non-Departmental sources on and after January 1, 1958, not in excess of 90% of the amounts specified in official provincial medical fee schedules; provided that
>
> (a) where exceptional skill is required because of complications or otherwise, or where a larger number of visits or a greater amount of time than

normal in an average case is required, the Department may pay extra remuneration; and

(b) where items are not included in the provincial schedule remuneration shall be computed in equity with procedures of similar responsibility and skill specified in the schedule."

Where a Departmental district is comprised of areas in more than one province, payment for medical services shall be made on the basis of the provincial schedule applicable at the place where the service was provided.

We were asked to arrive at an acceptable definition of the items termed "first visits" or "major office calls" in certain provincial schedules, and the following has been agreed upon. The rates set for these items will be used as a basis to pay for a visit when the patient is seen for the first time by the attending physician or when a patient, previously seen, presents himself with a new illness, when in most cases a complete physical examination, including urinalysis and hæmoglobin and sedimentation rate determination, with complete history and report, is carried out.

It was postulated early in the negotiations that provincial fee schedules should be stabilized for a period of three years for Departmental use and we are glad to advise that this stipulation no longer applies. Within the limits of Departmental estimates, account will be taken of periodic adjustments of provincial tariffs in the following manner, quoted from Dr. Crawford's letter:

"All Senior Treatment Medical Officers of the Department have been instructed to notify me of any upward revisions of provincial schedules after January 1, 1958. My approval will have to be obtained before departmental districts pay at the new rate, and the main consideration will be whether there are sufficient departmental funds for this purpose. It is the intention to pay at the revised rate at once if there are adequate departmental funds for the purpose, or alternatively to pay at that rate as soon as additional funds can be obtained. You will note that stabilization of provincial schedules for D.V.A. use for a period of three years is not a requirement. I believe also that our assurances to the Nova Scotia Division of your Association that their proposed new schedule would be used at once, can be implemented quite promptly by this procedure."

In summarizing the results of a protracted negotiation, it may be pointed out that a very significant advance has been made in the acceptance of the principle that payments to physicians shall be made on the basis of the official provincial medical tariff. Although it has not been possible to achieve our objective completely at this time, the removal of the 10% discount is a goal to be aimed at on the basis of favourable experience with the doctor-of-choice plan. The introduction of a degree of discretion to compensate for tariff adjustments is an unexpectedly favourable development and one which will do justice to those Divisions currently involved in major tariff revisions.

We count on the co-operation of all Divisions in interpreting the details of their respective tariffs to the officials of D.V.A. districts and in adjusting the difficulties which are likely to arise in the introduction of a new system of payment. We have assured the Minister of Veterans Affairs of the desire of the medical profession to afford to the entitled veteran the best medical care which we are capable of providing and of the active support of The Association and its Divisions in achieving this.

POSTGRADUATE MEDICAL AWARDS FOR CANADIAN DOCTORS

A unique publication has been prepared by The Canadian Medical Association, listing for the first time the grants, fellowships, bursaries and other forms of financial assistance available for postgraduate study to Canadian graduates in medicine. The compilation of this material has been a task which has not only involved a great deal of detailed work by the staff of The Association, but the helpful co-operation of a large number of fund-granting agencies throughout the world. Every endeavour has been made to ensure accuracy and completeness, but because of the nature of the material and the failure of some agencies to reply, the latter is not guaranteed.

Arranged alphabetically by field of postgraduate study, the pages of this reference manual list the nature of the award, its amount, the conditions which apply and the source of further detailed information.

Copies of the manual have been distributed to Canadian medical schools, to Divisions, to medical libraries and to appropriate educational bodies in the United Kingdom and the United States. Undergraduates may consult the office of their Dean of Medicine for access to the information listed.

A limited number of these manuals are available for members of The Association who are planning their postgraduate training, and a copy may be obtained on request to the General Secretary, 150 St. George Street, Toronto.

PUBLIC HEALTH

FLUORIDATION OF WATER

Although there is a continuous flow of material on water fluoridation for the prevention of dental caries in both the dental and the public press, little reference has been made to this topic in the *Canadian Medical Association Journal* of recent years. It is therefore appropriate to draw attention to a paper by Dr. J. M. Mather of the Department of Public Health, Faculty of Medicine, University of British Columbia (*Bull. Vancouver M. A.*, 34: 49, 1957). This article is designed to supply practitioners with facts which they can use to answer intelligently any questions put to them by patients, and also to convince those who have not taken an interest in the controversy of the merits of fluoridation.

It is obvious that dental caries is a major health problem, since dental surveys show that by the age of 12 or 13 the average child has five permanent teeth affected and in the late teens and twenties the number affected ranges from nine to 16. In addition, it has been shown that 8.8% of the total health expenditure in Canada in 1951 was for dental care, regardless of actual need.

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In addition to fluoridation, there are three factors involved in caries control. First is diet, for studies of European children during World War II showed that marked restriction of sugar temporarily reduced dental caries; return of refined carbohydrates to the diet rapidly increased the rate of decay once more. Secondly, it was proven in 1947 that toothbrushing immediately after intake of food and drink was useful in checking dental caries, though there is still no clear evidence of the value of any added material to toothpaste as a caries preventive. Thirdly, it would seem that if every child could be kept under adequate and continuous dental care from the age of three onwards much dental decay could be prevented; this ideal is interfered with through lack of awareness of need, cost of care, and shortage of dental manpower. Hence all these three factors have a part to play in control of dental decay, but cannot provide the solution to this important health problem. Dr. Mather shows that the history of the relationship of fluoride to dental caries goes back to 1908, and that no other health measure has received such long, complete and painstaking study. Results obtained from fluoridation have been amazingly consistent. There has been an over-all reduction of about two-thirds in the expected rate of caries incidence where children have drunk a mechanically fluoridated water at the recommended level of 1 p.p.m., throughout the period of enamel development, and a lesser reduction where such water was drunk for only a part of that period. Results obtained with naturally occurring fluorides and those added mechanically have been identical. Well-controlled studies have shown almost identical results; the best known is that of Brantford, Ontario, now in its twelfth year.

Dr. Mather states that there is absolutely no evidence that mechanical fluoridation at the recommended levels has any immediate or cumulative ill effects on human beings. For this there is a mass of factual evidence, including that from Brantford and the conclusive study of the United States Public Health Service. They found no evidence of unusual mortality or morbidity in a study of large population groups, half having drunk water containing fluoride, and half water free from fluoride. The only observable effect, mottling of teeth, takes place at a higher level than that recommended and is æsthetically rather than pathologically undesirable. In any case, millions of people have for generations drunk water supplies with a naturally occurring fluoride level well above that recommended. From the engineering viewpoint, there is no particular difficulty in fluoridating communal water supplies.

At present, 17 countries have municipalities with mechanically fluoridated water supply. In the U.S.A., 32 million people in more than 1500 communities use this type of water supply; in Canada 26 communities with a population of nearly a million fall into this category. Only Newfoundland, Prince Edward Island and New Brunswick are without such installations.

In considering methods of supplying fluoride, the problem is to provide protection against dental caries to all those who will benefit from it regardless of age, economic level or dietary habits. It must be made available from birth through the age of 16, and although there is no particular reason why it should not be put in table salt, milk, bread or toothpaste, water is obviously the most convenient carrier. Where it is not possible to provide a fluoridated water supply, topical application of fluoride by the dentist at intervals has proven to be efficient, but costs more in terms of money and personnel. The efficacy of introducing stannous fluoride into dentifrices is still under review.

Health authorities throughout the world have endorsed fluoridation of water supplies as an efficient, safe and practical method for the control of dental caries. These authorities range from an expert committee of the World Health Organization through national organizations like the C.M.A. down to authorities at the local level. Practically every national organization—medical, dental, public health, waterworks engineering—has gone on official record as approving of fluoridation, and no reputable organization of this type has ever questioned this measure. Certain individuals in the medical profession and in related groups have expressed opposition, but the really active opposition comes from the unorthodox and marginal healing groups, from the food faddists and from the pamphlet sellers. Such opposition follows the same pattern as that to other great health advances—pasteurization of milk, chlorination of water, and immunization. Because the influence of these groups on the confused layman can be serious, it is essential that medical and other similar groups see to it that the general public gets accurate information and is not misled by organized opposition.

Dr. Mather believes that eventually every municipal water supply in Canada will be fluoridated. This is only a question of time; opposition will probably slow it up but be powerless to prevent it. It is the duty of the general practitioner to identify himself as an active supporter of fluoridation rather than as a neutral observer. This he can do in two ways. The first and most valuable way is in daily contact with patients and their families. The practitioner should be well informed and positive in answering questions about fluoridation. His second responsibility is that of an influential citizen in the community. Because of this, it is the physician's responsibility to act as a source of accurate information to the public and to be ready in assisting organizations and societies in putting the facts before the public.

INFLUENZA

The second Asian influenza epidemic observed in Japan is decreasing; mortality rate is the same as in the first epidemic. The following information, dated December 11, is given by a W.H.O. virologist visiting Japan:

"The incidence has been relatively high in those areas which had a low incidence during the first epidemic last May-June. Areas heavily affected in the first epidemic have had a much lower incidence. A few second attacks confirmed by laboratory tests have been recorded. Everywhere the disease has occurred it has been mild with a low mortality rate. Incomplete figures suggest that the number of deaths attributed to influenza will be no higher in the second epidemic than in the first. The number of deaths in both epidemics is less than the number of deaths in the epidemic due to the Dutch-1956 strain in December 1956 to February 1957. No unusual clinical features have been noted. The effect on the normal life of the population has been of minor importance."

LETTERS TO THE EDITOR

BLOOD TRANSFUSION

To the Editor:

In the December 1 issue, I have just read an article by Dr. Bruce Chown of Winnipeg, regarding the danger of transfusions. This article I consider most timely, and coming from one as authoritative as Dr. Chown, it is doubly so.

I am one who had a large practice in the days before transfusions and did fairly well, I think. With the coming of transfusions a new era began, to be followed by the introduction of antibiotics. Both these are life-savers and, being new and expensive, met with immediate response by the medical profession (early in transfusion history the patient paid at least $25.00 for a transfusion). The operation was also very dramatic and being new and expensive "must be good". So transfusion and antibiotics became everyday treatment with resultant danger from staphylococcus and antibodies.

I know of one surgeon who stated at one time that he would not do major surgery on a patient whose hæmoglobin was below 70%. Just how many patients have developed hepatitis or other reactions, I do not know; perhaps he does not either.

One hospital I know of reported a greater number of transfusions for one month than had been given at the Toronto General Hospital the previous year. This was in the "hey-day" of transfusions.

I hope there are fewer now. I will be looking forward to Dr. Chown's further articles.

120-121 Medical Arts Bldg.,
Calgary, Alta.,
December 11, 1957.

H. A. GIBSON, M.D., C.M., F.R.C.S.(Edin.), F.R.C.S.[C.].

To the Editor:

I agree with Dr. B. Chown (*Canad. M. A. J.*, 77: 1037, 1957). Because I entered surgery before the flood of blood began, I am always amazed to see blood given for ordinary operations. It seems to be quite all right to take a pint of blood from a donor and let him walk home but wrong to lose a little blood during ordinary surgery! My belief is put into practice. In nearly 17,500 admissions to this general hospital we have not found it necessary to transfuse more than a dozen times. Our mortality rates compare favourably with those of other institutions.

Dr. Chown will appreciate the article "Chance, Design, and Discovery in Medicine" by J. H. Dible, Professor of Pathology, Postgraduate School, London, England. It is found in *The Postgraduate Journal*, Vol. 29, at page 59. Because so many of your readers are far from libraries, perhaps you will let me quote:

"Medical progress is a study of trial and error, of false paths, of whole generations under the sway of wrong ideas leading to wrong treatment and God knows what in the way of casualties—and the old tale yet goes on. A friend of mine said to me the other day, 'In the 18th century hundreds of people lost their lives through blood being taken out of them needlessly; today people are being killed through blood being put into them needlessly', and I—who only that morning had seen the body of a young man, dead as the result of an incompatible blood transfusion, given after an operation of convenience—could only agree with him sadly."

FRANK RIGGALL, M.A., M.D., F.R.C.P. & F.R.C.S.(Edin.), F.R.F.P.S.(Glas.)
Elizabeth Hospital,
Prairie Grove,
Arkansas, U.S.A.,
December 17, 1957.

OBITUARIES

DR. FERGUSON ROBERT LITTLE, aged 67, died on December 1, while a patient in the Halifax Infirmary. He had been in poor health for some years, and his fatal illness began on November 26.

Dr. Little had practised medicine in Halifax for 38 years. He was born in Halifax and was educated at Halifax County Academy. He graduated M.D., C.M., from Dalhousie University in 1914. In his youth he had been a great athlete, was captain of the Dalhousie football team, played inter-collegiate hockey, and was a star performer with the old Wanderers' English rugby team. He was a noted oarsman and fisherman, and until a few years ago enjoyed hunting. Dr. Little was always interested in community affairs and politics and was a past-president of the Nova Scotia Progressive Conservative Association.

He is survived by a son, Hugh R. Little; a daughter, Marion (Mrs. James Sutherland), Vancouver, and four grandchildren.

DR. MARION ROBERTSON O'BRIEN, aged 51, died suddenly in Halifax, N.S., on November 29. She had been in good health, and the fatal heart attack was sudden.

A native of Buctouche, N.B., Marion O'Brien graduated from the Dalhousie Medical School in 1927. She specialized in radiology and pathology in Charlottetown, P.E.I., until 1933, when she retired from active practice. Dr. O'Brien was interested and active in many things in the community and was a member of the I.O.D.E. During World War II she did voluntary work in the Navy League canteens.

Mrs. O'Brien is survived by her husband, Dr. Harry D. O'Brien; one son, John, a student at Kings Collegiate School in Windsor; a brother, K. C. Irving of Saint John, N.B., and a sister Dorothy (Mrs. George D. Watt) of New York.

DR. WILLIAM SHERMAN RODGER, 53, died at Cowansville, P.Q., on December 4. He was born at Masonville, P.Q., and was educated at McGill University where he graduated in 1929. After graduating he interned for three years at the Royal Victoria Hospital, Montreal, and in 1933 he became a general practitioner in Cowansville. Dr. Rodger served with the Canadian Army as a Major from 1941 to 1945 and was invalided home from England in 1943.

Dr. Rodger was keenly interested in the improvement of the Brome-Missisquoi-Perkins Hospital at Sweetsburg, P.Q., and was president of its medical board.

He is survived by his widow and one son.

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ABSTRACTS *from current literature*

MEDICINE

Proteins and Mucoproteins in Pleural Effusions.

H. H. ZINNEMAN, J. J. JOHNSON AND R. H. LYON: *Am. Rev. Tuberc.*, 76: 247, 1957.

This study demonstrates that all the major serum protein fractions are contained in pleural effusions in a distribution similar to that in the serum. Fibrinogen, however, may be decreased or absent in the aspirated fluid. Pleural effusions due to frankly inflammatory processes contain more total proteins than those due to neoplasms, *but there is a considerable overlap in the values.* The specific gravity of the pleural fluids examined in this study separated transudates from exudates less effectively than did the concentration of the total proteins. The total protein content of transudates usually is *below 3 g. per 100 ml.*, whereas that in exudates is greater.

The number of erythrocytes and leukocytes as well as the differential counts of the leukocytes in these pleural fluids appeared to be of little diagnostic value. The quantitative determination of mucoproteins in these pleural effusions failed to add information of diagnostic value. There was a good correlation between the amounts of mucoproteins and alpha$_2$-globulins in the effusions due to neoplasms, lymphoblastomas, and infections. This correlation held only to a less extent in the transudates.

S. J. SHANE

Roentgenographic Patterns in Histoplasmosis.

S. M. BRONSON AND J. SCHWARZ: *Am. Rev. Tuberc.*, 76: 173, 1957.

In this study 28 cases of histoplasmosis are presented with special emphasis on the varied roentgenographic appearance of the disease. Massive intrathoracic calcifications are more typical of infection with Histoplasma than with tubercle bacilli. The round lesions or granulomas of histoplasmosis contained calcium density in all of the cases. Presence of calcium is an important diagnostic consideration in a person from an endemic area.

In two cases, both in children, a diffuse infiltrate involving a pulmonary segment was observed. One infection pursued a benign clinical course; the other terminated fatally. The delayed process of clearing of these infiltrates, in one case up to four months, suggested unresolved pneumonia as well as tuberculosis.

The characteristic roentgenographic appearance of the primary infection in the young adults in this series was that of a small peripheral infiltrate. This was either resorbed after a few or several months or went on to calcification, in one such case after one year and two months. Hilar lymphadenopathy, either unilateral or bilateral, was always present.

Multiple discrete disseminated calcifications are characteristic scars of previous histoplasmosis. The roentgenographic appearance of histoplasmosis is probably diagnostically specific only in the diffuse miliary type, the large intrathoracic foci of calcification, and the "typical" splenic calcifications. In all other instances, e.g., round lesions, isolated infiltrates, disseminated or segmental infiltrates, hilar or mediastinal adenopathy, the diagnosis of histoplasmosis depends on additional evidence (skin tests, complement fixation tests, and culture or microscopic demonstration of the fungus, *H. capsulatum*). Massive pleural effusion is an unusual event in histoplasmosis. The presence of hepatosplenomegaly in infants and children is to be considered as highly suspicious of histoplasmosis in an endemic area.

S. J. SHANE

Serotonin and Antiserotonins. II. Clinical Studies, Especially in Essential Hypertension, with the Benzyl Analogue of Serotonin (BAS).

R. W. WILKINS AND W. HOLLANDER: *Circulation*, 16: 256, 1957.

Serotonin (5-hydroxytryptamine), a naturally occurring compound, is pharmacologically active on intravenous injection in man. It consistently raises the pulse rate but has a variable pressor, depressor, or biphasic effect on the arterial pressure. The mode of action of serotonin on these functions is not clear. Serotonin consistently and characteristically increases ventilation. However, it does not cause striking circulatory changes in the kidney although it usually produces moderate antidiuresis. The benzyl analogue of serotonin (BAS) (1-benzyl-2-methoxytryptamine), both intravenously and orally, reduces or prevents the symptoms caused by serotonin. Intravenously, BAS in addition has demonstrable "antiserotonin" effects on the characteristic blood pressure and respiratory responses to serotonin.

The benzyl analogue of serotonin alone, or in combination with other drugs, is antihypertensive in about 25% of patients with essential hypertension. It also causes moderate side effects of sedation, abdominal cramps, bradycardia, nasal stuffiness, and decreased libido, in this order of frequency. Whether its clinical effects in the dosage used orally in hypertensive patients are due to its antiserotonin qualities is not clear. BAS is a useful therapeutic agent in the management of some hypertensive patients.

S. J. SHANE

SURGERY

Tumours of Salivary Gland Origin in Children.

L. T. BYERS, LAUREN V. ASKERMAN AND E. PEACOCK: *Ann. Surg.*, 146: 40, 1957.

At Barnes Hospital in St. Louis, there were 23 cases of salivary gland tumour in patients under 18 years of age during 30 years, an incidence of 5% of such tumours. Of these, 17 were benign mixed tumours. Some had roentgen therapy previously without effect. Five of the parotid mixed tumours were recurrent. All were excised by a combined tumour-nerve dissection and none of those followed up recurred.

Six of the 23 salivary tumours were malignant, a similar incidence to that in adults. Two were undifferentiated. Five of the six had pain as the chief complaint and this seemed to be associated with the rapid growth, for the history was usually of only three to six months. Malignant tumours were usually larger than benign tumours. There was no facial palsy. Neither external radiation nor excision benefited three of the cases of adenocarcinoma.

One carcinoma was treated by radon seeds and the patient was well four years later. One mucoepidermoid carcinoma was excised with facial nerve preservation and the patient was well 14 years later.

Other tumours found were a Mikulicz syndrome, a plexiform neurofibroma, three hæmangiomas and two neurofibromas with multiple tumours elsewhere.

The advantages and dangers of preliminary incisional and needle biopsies and the technique of excision are discussed. BURNS PLEWES

Surgical Management of Acute Volvulus of the Sigmoid Colon.

D. B. HINSHAW AND R. CARTER: *Ann. Surg.*, 146: 52, 1957.

Sigmoid volvulus is second only to carcinoma as a cause of acute obstruction of the large bowel. It may be acute and fulminating in younger patients, or subacute and progressive in the elderly. In 75% the ileocæcal valve is competent and a double, closed loop obstruction exists. Arterial occlusion may occur rapidly and there is rapid immense distension of the rotated bowel loop. Venous occlusion leads to a tympanitic semi-rigid mass and hæmorrhagic infarction with shock. Radiographic examination often aids in diagnosis.

A series of 55 cases showed a drop in mortality from 65% to 26% with the advent of antibiotic therapy.

Treatment calls for the relief of obstruction and ultimate resection of the sigmoid. Transverse colostomy or cæcostomy has no place in definitive treatment.

Subacute volvulus when seen and treated early may be relieved by the proper use of a rectal tube, but the clinical differentiation of necrosis of the bowel and the frequent recurrence of the volvulus make it difficult and risky. Obstructive resection by the Mikulicz procedure is often the best technique if the bowel is gangrenous. If the torsion is successfully relieved by laparotomy or rectal tube, resection is necessary later. BURNS PLEWES

Hypophysectomy in the Treatment of Malignant Disorders.

R. LUFT: *J. Roy. Coll. Surgeons, Edinburgh*, 2: 256, 1957.

The problems involved in the technical aspect of complete and thorough hypophysectomy have been studied by Olivecrona of Stockholm and his associates. Cancer of the breast and prostate shows the property of hormone dependency and many patients are benefited by the removal of the gonads and adrenals. The removal of the pituitary gland suppresses the gonadotrophic and adrenocorticotrophic hormones; it also eliminates the possibility of the secretion of sex hormones from aberrant adrenal cortical tissue, the presence of which is demonstrable in 30% of autopsies. Moreover, hypophysectomy has induced remission in previously oophorectomized and adrenalectomized patients.

Remissions were obtained in 56% of women with metastatic breast cancer for an average of 17 months. It is found that the patients most likely to be benefited are those who showed a remission with other forms of hormone treatment. Investigations have shown that the excretion of œstrogens and androsterone, and thyroid function can be eliminated. But the adrenal medulla can still produce epinephrine after hypophysectomy. Polyuria disappears a few months after the operation.

BURNS PLEWES

THERAPEUTICS

Intrahepatic Obstructive Jaundice Following Chlorpromazine Administration.

E. E. WOLDMAN AND D. FISHMAN: *Ann. Int. Med.*, 47: 332, 1957.

A case is described of intrahepatic obstructive jaundice developing two weeks after the ingestion of only 75 mg. of chlorpromazine. Hyperbilirubinæmia and marked elevation of the alkaline phosphatase and total cholesterol, with a negative cephalin flocculation test, characterized the chemical investigation. The peripheral blood showed a transient eosinophilia. A liver biopsy was performed.

The relation between drug ingestion and the appearance of jaundice is suggestive of hypersensitivity, and the reaction depends upon the individual's sensitivity to the drug rather than upon the total amount taken. It is suggested that physicians who prescribe the use of chlorpromazine should administer this drug for one or two days and then wait two weeks to determine whether a hypersensitivity to this drug is present. S. J. SHANE

DOCTOR-PATIENT RELATIONSHIP OR DOCTOR-PUBLIC RELATIONSHIP

(Continued from page 131)

to accept. We must not allow anything to threaten the doctor-patient relationship. It is a beautiful thing and has stood as a model through the ages. At present, younger scientific disciplines look to it for guidance.[19]

SUMMARY

This paper is a critical discussion of the current public relations program. It is suggested that in its present form this program will tend to distort unfavourably the public's viewpoint of the Canadian doctor.

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PROVINCIAL NEWS

BRITISH COLUMBIA

The University of British Columbia is conducting a campaign for funds, sorely needed for bare existence. Medicine, law, engineering, arts are all suffering badly for lack of room of living space, of laboratories, and of buildings to house students. A U.B.C. Development Fund is being opened; the government of B.C. in addition to its usual grants has promised to match dollar for dollar any sum collected up to $7500.

It is of great interest to follow the history of contributions made by students themselves to this university in the past 25 years. During that time they have contributed $3,000,000 and are still giving, at the rate of $5 each annually. They have built playing fields and a gymnasium, and have contributed to all sorts of activities. Dr. Norman MacKenzie, President of U.B.C., says "I know of no university anywhere to which students have contributed so much out of their own limited resources."

The B.C. Cancer Foundation held its 22nd Annual Meeting on November 27. Some of the reports given are of great interest. Mr. Donald F. Farris, Chairman of the Campaign Committee, reported that the 1957 campaign collected $311,676; of this amount $80,000 will be spent on capital construction.

Dr. A. M. Evans, Director of the B.C. Cancer Institute, reported 65,813 examinations and treatments given during the clinical year. He dwelt on the urgent need for more beds, staff and equipment.

Mr. W. H. Mowat was elected President for the coming year.

Grace Hospital in Vancouver is to have a $500,000 addition, which will add some 30 beds and many badly needed facilities to this hospital, which is one of the many activities of the Salvation Army. Grace Hospital is one of the chain hospitals where clinical instruction is given for the medical course of U.B.C. and is entirely devoted to women's diseases and obstetrics. It has grown steadily with Vancouver, from an eight-room house to a thoroughly modern hospital.

There has been a great deal of discussion lately in the press of British Columbia, and we suppose elsewhere as well, regarding the dangers of radiation, so that the public has begun to question the advisability of such measures as chest radiography and radiography for other diseases. In this connection Dr. Kincade, Director of Tuberculosis Control for B.C., has done good service by definite pronouncements on the subject. He does not make light of the dangers of radiation—but he points out that health and radiological authorities are perfectly cognizant of these dangers and are quite able to control them: and that the danger of chest radiography, for instance, is extremely slight, and is far outweighed by its value. He decries "useless" radiography, such as is used for shoe-fitting, we are glad to see.

Mr. Jeffrey D. Burton, Med. '58 (U.B.C.), has been awarded the annual $500 bursary of the B.C. Division of the Canadian Cancer Society. Mr. Burton, who graduates next year, is a Penticton-born British Columbian.

The Seventeenth Annual Meeting of the Medical Services Association (M.S.A.) was held on December 13, following a dinner at Shaughnessy Golf Club. The reports have been issued, and show steady growth; the present membership is 384,093.

The M.S.A. building is being considerably enlarged and will be ready for occupation early in 1958.

J. H. MACDERMOT

SASKATCHEWAN

Saskatchewan's ninth public health region, to be known as the Yorkton-Melville Health Region, came into existence this month, after publication of formal orders by the Health Minister, the Honourable Walter Erb.

Steps will be taken as soon as possible to call a meeting of representatives from all urban and rural municipal governments in the Health Region who are to compose the Regional Council. After an initial organizational meeting the body will meet annually. The Regional Board will meet each month.

As a further step the Department of Public Health will have the responsibility for the recruitment and appointment of a medical health officer or other staff.

Enrolment at the University of Saskatchewan this year is 9023 or 15.3% higher than last year, according to the annual report issued recently. This increase, far greater than expected, produced what the University terms "a crisis of numbers".

The report showed that enrolments had been growing steadily since 1953, but the total of more than 3000 full-time degree students attained last year was not anticipated in earlier estimates until 1960.

The trophy originally presented during the First World War for medical efficiency will once again be up for competition. The Ross Efficiency Trophy was donated by Brigadier A. E. Ross, Commander of the Canadian Corps in France during the First World War. In 1917 it was won by the 10th Canadian Field Ambulance under command of Lieutenant-Colonel T. M. C. Leask. Recently Dr. Duff Leask, a Moose Jaw dentist and son of Lieutenant-Colonel Leask, advanced the suggestion that the trophy might be of some use to present-day army units.

Lieutenant-Colonel R. B. C. Cawsey suggested to higher authorities that medical units of the Prairie Command might compete for the plaque. This suggestion has been accepted along with the trophy. It is planned that it will be awarded to Prairie Command Units selected to compete in the Ryerson and Shillington Trophy Competition.

Marking the end of its first half century of teaching, research and public service, the University of Saskatchewan will celebrate its Golden Jubilee in 1959.

Four occasions will highlight the main activities—University Farm and Home Week in January; Convocation in May; meetings of Canada's learned societies in June, and celebrations on the actual anniversary dates of registration and first lectures in September 1909.

On September 28, 1909, 70 students registered in arts and science in the first class at the University; in 1959 an expected 12,000 students will use the

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facilities of the ten university colleges and two schools during the winter term, summer school, or correspondence classes; many more will attend short courses, forward problems, or pay visits to the University, for this institution has become one of major community interests.

On the 1620 acres of prairie and bush granted to the University, the pioneers of the past 50 years have built a campus of grey stone and brick buildings, university farm and playing fields.

Mr. Justice E. M. Culliton of Regina is Chairman of the Jubilee Committee and the Vice-chairman is President W. P. Thompson. G. W. PEACOCK

MANITOBA

The hospital at Shoal Lake, which twice has been destroyed by fire, has been rebuilt and opened recently. Dr. S. Bardal, the veteran doctor, declared the building open.

At the annual meeting of the Council of the College of Physicians and Surgeons of Manitoba, the following officers were elected: President, Dr. R. E. Dicks, Dauphin; Vice-President, Dr. A. R. Birt, Winnipeg; Treasurer, Dr. T. H. Williams, St. James; Registrar, Dr. M. T. Macfarland, Winnipeg.

The new wing of Misericordia General Hospital was on view during open-house week, December 9 to 13. The medical profession was received on the evening of December 9.

Dr. Stuart L. Carey, medical superintendent of Clearwater Lake Sanatorium, has gone to Chicago to take a course in bronchoscopy at the University of Illinois. ROSS MITCHELL

ONTARIO

The Ontario Society for Crippled Children has drawn up plans for a new treatment and rehabilitation centre in Toronto. The society intends to build a 105-bed centre on a 10-acre property near Sunnybrook Hospital. Persons treated will be those suffering from cerebral palsy, poliomyelitis, paraplegia, spina bifida, muscular dystrophy, and accident victims. There will be special departments of physiotherapy, occupational therapy, hydrotherapy, speech training, play school and parent instruction.

The centre will have a swimming pool and will provide accommodation for patients now attending two cerebral palsy clinics in Toronto. The swimming pool will be available for blind swimmers from the Canadian National Institute for the Blind. A motel will be provided for parents who must stop over in Toronto.

Dr. Tage Astrup of the Carlsberg Foundation Biological Institute, Copenhagen, addressed the Physiological Society of the University of Toronto in November on "Relationships between blood coagulation, fibrinolysis and arteriosclerosis".

Dr. Gordon Copping, Assistant Professor of Medicine, McGill University, addressed the November meeting of the Essex County Medical Society on "The present status of thyroid therapy". This society in the past year has provided five radio broadcasts on cancer, one on physiotherapy and one on poison.

The Poison Control Centre opened in Windsor on November 27. Mayor Patrick declared December 1-8 "Poison Control Week" and the local pharmacists distributed 5000 copies of a booklet on "Common poisons in the home". LILLIAN A. CHASE

NOVA SCOTIA

The annual staff dinner of the Victoria General Hospital was held at the Lord Nelson Hotel, Halifax, N.S., on the evening of November 19. The President, DR. E. F. Ross, presided. The guests were the Honourable R. L. Stanfield, Q.C., Premier of Nova Scotia, and Mr. Manuel Zive, Chairman of the Hospital Commission. This staff dinner was well attended. There were few absentees.

After a brief address by the Premier, the Honourable R. L. Stanfield, Mr. Manuel Zive spoke about the contemplated new Victoria General Hospital construction. He stated that it was the hope of the Hospital Commission that the provincial government would be able to undertake, in the near future, the construction of an entirely new building which would be attached to the present Victoria General Hospital in the form of a wing. Mr. Zive pointed out that the plans called for the addition of 615 beds, and this together with the present number of beds would bring the over-all total to 1000. This proposed building calls for new operating rooms, much larger than the present ones, and in the interests of economy, calls for large wards of the public ward variety. Mr. Zive also pointed out that it would take a year to fully develop the plans, and somewhere between one and one-half to two years in the construction of this new building, if approved.

The shortage of hospital beds at the Victoria General Hospital has been in evidence for the past three years. With the advent of national hospital insurance, further burdens of accommodation would be thrown upon the hospital. The full impact of hospital insurance cannot at the present time be visualized, but it is the opinion of the hospital administration that the new hospital building when completed should fulfil requirements.

The entertainment provided by the entertainment committee of the staff consisted of a showing of a number of Kodachrome slides taken by staff members. There was an excellent response to requests for these colour slides and some little time was taken up in the viewing of them. The judges, under the chairmanship of Dr. H. Schwartz, were, owing to the excellent quality of the slides, hard pressed to declare a winner. Dr. N. H. Gosse carried away top honours with his coloured slide of the "Bridge of Sighs", taken while he was in Venice this past fall. Dr. W. Stevenson, with the assistance of Dr. D. Roy, provided entertaining piano selections. All in all, it was a most enjoyable evening. WALTER K. HOUSE

NEW BRUNSWICK

The American College of Surgeons at the Annual Convocation held in Atlantic City awarded fellowships to three Saint John surgeons: Dr. Harold J. Rosen, Dr. W. D. Miller and Dr. T. A. Foster; all of

these are already Fellows of the Royal College of Physicians and Surgeons of Canada.

Dr. W. B. Howatt, until recently radiologist at the Prince County Hospital at Summerside, P.E.I., has accepted an appointment as radiologist at the Hotel Dieu Hospital at Chatham, N.B., and at the Miramichi Hospital at nearby Newcastle.

Two towns in northern New Brunswick are spending two million dollars to provide increased hospital facilities. In Chatham the Hôtel-Dieu has a new wing nearing completion, costing one and a half million, and next year the Miramichi Hospital in Newcastle will also add a new wing to their plant, expected to cost $475,000.

The Saint John Medico-Legal Society held its annual meeting on December 3 in the Provincial Laboratory auditorium. Dr. G. W. A. Keddy presided. A film "The Medical Witness" was shown and was followed by a panel discussion on medico-legal problems. Panel members were Dr. H. A. Bird, Dr. R. A. Gregory, Dr. Norman Skinner, Mr. J. Paul Barry, Q.C., Mr. Norwood Carter and Dean W. F. Ryan. Questions from Medical and Legal Society members were discussed and an unusually pleasing and informative evening was enjoyed by a large audience.

Dr. Alan Ross, Professor of Pædiatrics, McGill University, spoke on "Pædiatrics in Russia" at a meeting of the Saint John Medical Society in November and discussed clinical problems in the children's wards of the Saint John General Hospital.

Dr. H. I. Goldberg, dermatologist of Halifax, presented a paper on "Recent advances in dermatological therapy" at St. Stephen and the Hôtel-Dieu Hospital, Perth, N.B., on successive days. As usual, the subject of skin disease assured an interested audience.

Dr. B. H. Kanter of Moncton has been appointed coroner for Westmorland County.

Dr. J. L. Giovanetti has returned to his home in Newcastle after being in hospital at Moncton.

A. S. KIRKLAND

NEWFOUNDLAND

In an unexpected public statement on December 13 the Premier of Newfoundland announced an extension of the services to be offered to children under the provincial government's Children's Health Plan. This plan was promulgated in the fall of 1956 and its first stage went into effect on January 1, 1957. This provided for free hospitalization, including laboratory and x-ray diagnostic services and drugs, as well as for outpatient diagnostic services performed in hospital, for all those under the age of 16. The total cost is said to have been about $1,000,000 in the first year.

It is intended to put the plan into operation in several steps, which will later include the provision of home medical care and all other types of health service. Under the second stage, physicians' and surgeons' services to hospital in-patients will also be paid for by the public treasury. The Premier stated that negotiations with the medical profession concerning a schedule of fees had not yet begun, but that he hoped they would be completed in time to allow this stage to start on February 1.

About 170,000 people will be covered in this Children's Health Plan, at an estimated annual expense of $1,500,000 when this second stage comes into operation.

At the present time a majority of children in this province are already included in the Cottage Hospital Plan which furnishes complete medical care to more than half of the population throughout most of the province, but excluding St. John's, the Bay of Islands area including Corner Brook and Deer Lake, Buchans, portions of Bonavista, Trinity and Conception Bays, and the eastern and southern shores of the Avalon peninsula. This is a government-subsidized prepayment insurance scheme and is administered for the most part directly by the Department of Health. Since this Plan will now cover adults only, a reduction in the annual family premium has been made.

It is expected that the burden of these additional public expenditures will be eased by large federal grants to this province in 1958. These include the grants-in-aid to the Atlantic provinces recently proclaimed by the Prime Minister of Canada, and payments that are anticipated under the 1949 Terms of Union and now under study by a Royal Commission. Besides these, the nation-wide hospitalization scheme is believed to be imminent, and, in this, about 70%

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of the costs in Newfoundland will be borne by the federal government.

Several physicians from this province travelled to Toronto in the past month to take the oral portions of the examinations of the Royal College, and all were successful in obtaining their Certificates. They are: Dr. John Bennett (Obstetrics and Gynæcology), Dr. John Collins (Pædiatrics), Dr. Patrick McNicholas (Ophthalmology), and Dr. Patrick Whelan (General Surgery).

Personal News:

Dr. Gerald Buckingham has taken up private practice on Bell Island, following completion of a period of service as medical officer with the Department of Health in St. John's. This brings the number of practitioners on the island to five, including Drs. Rufus Dominic, B. J. Egan, Walter Templeman, and James Wilson.

Conception Bay has obtained the services of two new physicians, Drs. Arthur A. Moores and Lionel D. Young. Dr. Moores, a graduate of the College of Medical Evangelists in Los Angeles, has been practising in St. John's in association with Dr. E. W. Hildebrand for the past two years. He will be in Brigus. Dr. Young, who is a native of St. John's, completed his internship at the General Hospital in October, and received his degree from Trinity College, Dublin. He will be the first resident practitioner at Spaniard's Bay.

Dr. Norman Rutherford, who was formerly in charge of the Cottage Hospital at Brookfield, has resigned to take up practice at Buchans. His position will now be taken by Dr. Wilfred Evans, who will move from Burgeo. Dr. J. M. Calder, previously Assistant Medical Officer at Brookfield, will become superintendent of the hospital at Burgeo.

A. J. NEARY

CANADIAN ARMED SERVICES

The following R.C.N. medical officers have successfully completed the examinations of the Royal College of Physicians and Surgeons for certification in Internal Medicine: Surg. Cdr. R. H. Roberts, R.C.N., Chief of Medicine, R.C.N. Hospital, Halifax, N.S.; Surg. Lcdr. C. A. West, R.C.N., Chief of Medicine, R.C.N. Hospital, Esquimalt, B.C.; Surg. Lcdr. D. W. Brooks, R.C.N., serving on medical staff, R.C.N. Hospital, Halifax, N.S.

The appointment has been announced of Lt.-Col. N. H. McNally and Lt.-Col. R. Feuiltault to the acting rank of Colonel while employed in their specialty.

Wing Commander K. W. Hampson has completed a postgraduate course at the Harvard School of Public Health and has taken up duties with the Director General Medical Services (Preventive Medicine Branch), at Air Force Headquarters. He replaces Wing Commander W. W. Laughland, who has proceeded to the School of Hygiene, University of Toronto, for a course in industrial hygiene.

BOOK REVIEWS

OBESITY: ITS CAUSE, CLASSIFICATION, AND CARE. E. Philip Gelvin, New York Medical College and Metropolitan Hospital, New York, and Thomas H. McGavack, New York Medical College. 146 pp. Illust. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York, 1957. $3.50.

This small book is well worth reading and owning. In it are given adequate discussions of the physiology and pathology of obesity, a condition which exists only in *Homo sapiens* and his domestic animals but not in any wild creature—no doubt the wild animals who become too fat are eaten by some predator. Perhaps nations who become too fat will also be eaten—purely metaphorically of course—by some predator. Obese people are potentially sick people, and they can be healthier if they eat less. The authors clearly stress that obesity, as a problem in public health, is caused by only one situation, and that is gluttony. Glands are not involved except in rare cases. Thyroid preparations are not only ineffective but harmful: they depress normal thyroid function, a circumstance described by Johnston, Squires and Farquharson, of Toronto, as far back as 1951. For weight reduction mixed diets of 1000-1200 calories per day are suggested. In addition the patient must be seen by the physician at least as often as every two weeks; if not, he will fall again into evil ways. Amphetamine preparations are found to be useful, as are 11-oxycorticoids in certain rare situations. In general the approach to obesity in this book is realistic and forthright.

MUSCLE RELAXANTS IN ANESTHESIOLOGY. Francis F. Foldes, University of Pittsburgh School of Medicine. 210 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $6.00.

This book gives a very clear and concise account of the use of muscle relaxants in anæsthesiology. The separation of these into nondepolarizing and depolarizing agents serves a useful purpose. The chapter on physiology is good, as are also those on pharmacology and the use of antagonists. The directions for the use of the different preparations are clear, and also the complications and their treatment. Almost everyone will agree with the author's opinion that succinylcholine so far most nearly approaches the ideal relaxant, but could still be improved upon.

This book would be a very useful addition to any hospital medical library and should be read by all anæsthetists.

THE MENTALLY ILL CHILD. A Guide for Parents. Steven B. Getz, California School for the Deaf, Berkeley, and Elizabeth Lodge Rees, Hayward, California. 88 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $3.75.

Described as the first book written for parents of children diagnosed as schizophrenic, autistic, or severely emotionally disturbed, this is the work of a psychologist and a pædiatrician. The authors point out that such children are among the last groups of the handicapped to receive the attention of so-

ciety, and they pay tribute to the valuable efforts now being made on their behalf by the League for Emotionally Disturbed Children. Much useful information is packed into the book, with a quite extensive bibliography. The last four chapters (Your attitude towards your child, The child at home, Choosing facilities for your child, and The league idea) are particularly instructive and likely to hearten parents endeavouring to cope at home with a mentally ill child or seeking the best residential facilities, although it is made abundantly clear how scarce these facilities are. It is also claimed that the book is of value to all professional specialists who come in contact with these children and their families for diagnosis and guidance. For guidance, yes; before satisfying the former criterion, however, some expansion of the chapters on diagnosis and case-history would be desirable. Still, as a book primarily intended for parents it will undoubtedly serve a useful purpose, not least in its assurance that their problem is neither unique nor necessarily hopeless.

THE WINNIPEG GENERAL HOSPITAL SCHOOL OF NURSING, 1887-1953. Ethel Johns. 87 pp. Illust. 1957. $2.00.

Future generations of Canadians will find themselves under a debt to those devoted souls who are taking upon themselves the task of recording the history of some of our institutions from the records available and the memories of our senior colleagues. Dr. Ethel Johns has compiled an admirable history of the Winnipeg General Hospital School of Nursing, which is now 85 years old. She has had access to the archives of the hospital, and also had the opportunity of discussing history with many of those still connected with the hospital or previously associated with it. It might be added that this work has been given freely by Dr. Johns to the Alumnæ Association of the Winnipeg General Hospital School of Nursing.

She begins the story in December 1872, when the typhoid-ridden hamlet of Winnipeg was an inconvenient place for the sick, and at a public meeting foundations were laid for the acquisition of some very primitive accommodation for a hospital of 12 beds. There were a few physicians in the community, but there were no nurses and the patients had to help each other as best they could. In a later search for better surroundings, the hospital was transferred no less than six times until at last a suitable site was acquired between Bannatyne and McDermot Avenues, where the Winnipeg General Hospital now stands. For the erection of the hospital itself, the energy of the Red River women was responsible, but even at this time there were no nurses; these appeared only with the appointment of the first matron in 1880. In 1884 the first really suitable Winnipeg General Hospital was constructed. From then on Dr. Johns carries the story through to the opening of the present palatial school of nursing.

The book is one more to add to the shelf of books essential to the student of Canadian medical history. It remains to be added that it is well written and eminently readable.

(Continued on advertising page 48)

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BOOK REVIEWS

(Continued from page 161)

MENTAL HEALTH ADMINISTRATION. Jack R. Ewalt, Harvard Medical School, Boston, Mass. 168 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $6.00.

This book deals with the total administration of a mental health department, including mental hospitals and psychiatric clinics, the details of which are set forth clearly and distinctly. The results of treatment in the state of Massachusetts are good. This state, while small in area, has a population about the same as that of Ontario and would therefore be dealing with a mental hospital population in excess of 20,000.

Practically every aspect of the organization in the central government office as well as in the individual hospital is outlined in detail with well-defined channels of communication. Recommendations are made on ward layout, and the kinds of floors and windows, etc. Details of ward administration are precise and well presented. Considerable space is devoted to the organization of ancillary medical services within the hospital, and details of the functioning of an outpatient department or a community mental health clinic. Since the section on medico-legal aspects, particularly medical evidence in court, is all based on English law, most of the points made are equally applicable to this country.

The theme of the book is the mental hospital as a therapeutic community with every part of it directed to the benefit of patients rather than to administrative convenience, the mental hospital being well integrated into, and accepted by, the community it serves. Morale as a necessary entity in a therapeutic community is well interwoven into the organization, and although morale is a subtle quality it is well defined.

The point is well taken that the administrative structure of the mental hospital is clearly reflected in the final treatment results. Practically every item in this easily readable book is equally applicable to every mental health department and every mental hospital in Canada as a detailed guide to good and effective administration, broadly based on time-tested business principles.

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BOOK REVIEWS

(Continued from page 48)

HOW TO USE A MEDICAL LIBRARY: A Guide for Practitioners, Research Workers and Students. Leslie T. Morton, Information Officer, British Medical Journal. 53 pp. 3rd ed. William Heinemann Medical Books Ltd., London; British Book Service (Canada) Ltd., Toronto, 1957. 7s.6d.; $1.30.

One of the indispensable skills for any student of science, whether undergraduate or research worker, is the proper use of library and bibliographic facilities. Every medical student should be taught—though many still are not—how to use his library and its contents, particularly the indexes and periodicals. Mr. Morton's essay, which now appears in a third edition, is designed to guide the British medical student or practitioner through the maze of reference services, and fulfils this task admirably. Anyone proposing to use the medical libraries of Britain would be foolish not to purchase a copy.

Canadians can also benefit from reading the book, but must remember that, for example, our system of citing references is different. Perhaps Mr. Morton can find a collaborator here or in the United States, to add a chapter on our chief libraries as a supplement to the excellent data given on U.K. ones.

WOMEN DOCTORS OF THE WORLD. Esther G. Pohl Lovejoy. 413 pp. Illust. The Macmillan Company, New York; Brett-Macmillan Ltd., Toronto, 1957. $5.95.

Medicine undoubtedly began at home as a service rendered by women to their families and to the sick of the communities in which they lived. There is a charming blend of fact and fancy in the stories regarding the medical activities of women in ancient lands. During the Græco-Roman period there were women doctors, Christian and pagan, not only in Rome but also in the provinces—European, African and Asiatic. At an early stage in its development medicine was largely a family vocation. Medical men depended upon the help of their wives, daughters and sons. There were women on the faculty of the first secular medical school of the first university in Europe, at Salerno—including Trotula, the greatest woman doctor of the Middle Ages. Famous midwives practised and taught obstetrics and wrote books for the guidance of their sisterhood, and the royal midwife was a personage.

Across the ocean, in the New World, men and women cared for

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BOOK REVIEWS

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the sick without benefit of regular training until 1765, when the first North American medical school was opened in Philadelphia. Women were not admitted. It was about 1850 that the medical education of women became manifest as a vital part of the feminist movement in the United States and in England. In that year the Female Medical College of Pennsylvania, supported in large measure by Quakers, opened its doors in Philadelphia. In the same decade hospitals staffed by women were opened in New York and Boston. Emily Stowe of Toronto (1831-1903), the first Canadian woman doctor, was of Quaker origin; she went to New York, where she enrolled in the Medical College and Hospital for Women (homœopathic). Her daughter, Augusta Stowe Cullen, was the first woman to receive a medical degree in Canada—this was in 1879. In England, Elizabeth Garrett Anderson received her Licentiate of the Society of Apothecaries in 1865 and in June 1870 took her degree at the University of Paris; while in Edinburgh, Sophia Jex-Blake led the struggle to have the University open its doors to women, finally accomplished in 1869.

In this book the story of women's medical education in Europe and the Near East is given in detail, country by country. Medical education in the Far East for both men and women has been influenced by medical missionaries; and it is interesting to note that there are now 4452 women physicians in India.

During World War I the offer of service by the Scottish Women's Hospitals was originally turned down by the British but accepted by France, Serbia, Greece and Russia. As members of the Women's Hospital Corps of England they worked directly with the French Red Cross, but the Corps was later recognized by the British War Office. The American Women's Hospitals had hardly started their work when the Armistice was signed, but afterwards they continued in Serbia, Greece, Turkey, Armenia, Russia, Albania and Japan; work in Macedonian Serbia was completed in 1934, but the organization stayed on in Greece until 1941, during World War II. During this later war there were 700 women doctors with the Royal Army Medical Corps alone. In the occupied countries many women doctors were sent to concentration camps—one of them, Dr. Charlotte Ruys, released from prison when Holland was liberated, became dean of the Medical Faculty of the University of Amsterdam.

This is but part of the story of women in medicine; and all those concerned with medical education will be interested in this book written by a woman doctor.

ATLAS OF TUMOR PATHOLOGY, Section VIII, Fascicle 30. Tumors of the Kidney, Renal Pelvis and Ureter. Balduin Lucké, Late Professor of Pathology, University of Pennsylvania, Philadelphia, Pa., and Hans G. Schlumberger, Professor of Pathology, Ohio State University, Columbus, Ohio. 208 pp. Illust. Armed Forces Institute of Pathology, Washington, D.C., 1957. $2.25.

ATLAS OF TUMOR PATHOLOGY. Section X, Fascicle 36. Tumors of the Pituitary Gland and Infundibulum. James W. Kernohan and George P. Sayre, Mayo Clinic, Rochester, Minnesota. 81 pp. Illust. Armed Forces Institute of Pathology, Washington, D.C., 1956. $1.00.

ATLAS OF TUMOR PATHOLOGY, Section X, Fascicle 38. Tumors of the Eye and Adnexa. Algernon B. Reese, Institute of Ophthalmology, New York City. 205 pp. Illust. Armed Forces Institute of Pathology, Washington, D.C., 1956. $2.00.

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BOOK REVIEWS

(Continued from page 54)

These are three additional volumes in the series entitled "Atlas of Tumor Pathology" that will encompass when completed the entire field of tumour pathology. The authors have endeavoured to utilize as fully as possible the researches of the last several years, and, in so far as these have given new facts and represent actual advances in our knowledge of pathological processes, to incorporate them into the contents of these fascicles. Their greatest value is in that they record the natural history, the histogenesis, the gross and microscopic appearances and the prognosis of all the known tumours—benign and malignant. Principal use has been made of the enormous amount of pathological material from the Armed Forces Institute of Pathology, and the great number of illustrations and reproductions—black-and-white and also colour — are superb. These fascicles give the most complete and practical information on the entire field of tumour pathology for the pathologist, the surgeon, and all who need to consult a textbook.

BRONCHIECTASIS: Radiological Diagnosis and Prognosis after Operative Treatment (Acta Radiologica Suppl. 143). Carl Einer Gudbjerg, Department of Radiology, University Hospital, Copenhagen. Translated by Anna la Cour. 135 pp. Illust. Acta Radiologica, Stockholm, 1957. Sw. Kr. 25.00.

This is an interesting approach to a subject that has been discussed freely for many years. The preoperative diagnosis and postoperative results, as indicated on radiography and particularly bronchography, are carefully considered. There is also a full discussion of technique and prognosis. The author uses the bronchographic findings to assess the results of operative treatment, but admits that these alone are not sufficient.

On the whole, this is a good review from the standpoint of radiology; the case reports are carefully tabulated and the conclusions are very fair.

AN ATLAS OF MUSCLE PATHOLOGY IN NEUROMUSCULAR DISEASES. J. Godwin Greenfield, G. Milton Shy, Ellsworth C. Alvord and Leonard Berg; from the Department of Health, Education and Welfare; Public Health Service; National Institutes of Health; and National Institute of Neurological Diseases and Blindness, Bethesda, Maryland. 104 pp. Illust. E. & S. Livingstone Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1957. $7.65.

Transmission of neuropathological detail by reproduction of coloured photomicrographs can nowhere be better exemplified than in this excellent and much needed atlas. The clinical value of many muscle biopsies has long been questioned by clinicians and pathologists alike: this comprehensive atlas helps to fill the need for a handy visual reference to the pathological variations seen in neuromuscular disorders in the human being. The book is sensibly divided into two sections, the first dealing with the histopathological findings in diseased muscle and the second part correlating the pathological findings with a clinical classification of neuromuscular disease and with brief representative case histories. The text is brief and factual and in no way detracts from the many excellent figures that are thankfully large and show comprehensive detail. Also collected in table form are differential diagnostic groups of cases demonstrating the frequency of the various histopathological abnormalities noted in each clinical subdivision of the neuromuscular diseases.

This well-married combination of pathological and clinical data, so ex

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BOOK REVIEWS

(Continued from page 58)

cellently illustrated, is unhesitatingly recommended for all pathologists and those clinicians dealing with neurological and muscular disorders.

SUGGESTIVE THERAPEUTICS. H. Bernheim, Faculty of Medicine, Nancy; translated by Christian A. Herter, New York. 420 pp. Reprinted by Associated Booksellers, Westport, Conn., 1957. $5.95.

This book represents a treatise on the nature and uses of hypnotism. It is a reprinting of the original American translation first published some 70 years ago. The author gives first a detailed account of the methods employed in inducing hypnotism and the different manifestations which may be determined in hypnotized subjects. There is a very good discussion of theoretical views regarding hypnotism, and the author states his personal opinions regarding the psychological and physiological mechanisms of this phenomenon. He relates the state of hypnotism more closely to sleep than to hysteria, although this view is not supported by electro-encephalographic tracings taken during the hypnotic state. The applications of the doctrines of suggestion to psychology, legal medicine, and sociology are discussed. Finally, there are numerous detailed examples of personal observations of the value of hypnotism in various clinical conditions. Some of the suggestions are of particular interest in terms of our present more comprehensive understanding of the physiology of the nervous system.

This book should prove of interest and value to every physician in view of its numerous theoretical considerations and the suggested applications, and more especially because of the more recent revival of medical hypnosis: even the medical sceptic will find numerous thought-provoking theories in this well-written study.

INFORMATION THEORY: Papers presented at the Third (London) Symposium, September 1955. Edited by Colin Cherry. 401 pp. Illust. Butterworth & Co. (Canada) Ltd., Toronto, 1956. $11.50.

The term "information theory" originally indicated a field where probability theory and telecommunication met; this has since widened so that, for example, Nobert Wiener's "cybernetics" and von Neumann's "theory of games" might be considered to belong, if not in, at least near, this field. The scope of information theory can be judged best by looking through the contents of this book, where some intriguing titles appear—for example, "Negative entropy of Welsh words", or "Mathematical theory of word formation".

Several of the problems reach into the field of medicine, as the information is supposed to be absorbed via some human sense organ. One-fifth of the book, therefore, contains contributions on "Meaning and the human senses" and another fifth deals with "Behaviour and its mechanism": the contributors to these papers are electronics- and telephone-engineers, psychologists, and anatomists.

The book seems to be of little importance to most physicians. It is only for specialists interested in electronic brains, neurologists and psychologists interested in electric circuits, and physiologists who read the works of von Helmholtz that this volume may contain something of interest.

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BOOK REVIEWS

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ENVIRONMENT AND THE DEAF CHILD. Steven Getz, Audiologist, California School for the Deaf, Berkeley, California. 173 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $4.00.

This book discusses some very controversial problems in the education of deaf children and analyzes the pros and cons in an unemotional and statistical manner. It is a book that should be read carefully by those interested in the education of the deaf child. Its chief value should be in encouraging a more intelligent balance in the use of the manual and oral methods in schools for the deaf, so that the main objective can be obtained—that is, an independent and well-adjusted citizen.

NEW RESEARCH TECHNIQUES OF NEUROANATOMY. Edited by William F. Windle, National Institute of Neurological Diseases and Blindness, Bethesda, Md. 98 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1957. $5.25.

Looking back over the past decade of medical publishing, one is impressed by the enormous outpouring of monograph-sized books that are simply edited reports of brief symposia dedicated to rather narrow fields of learning. This phenomenon is both good and bad: good because it throws the discussion open to a much larger "audience"; bad because the great majority of these "books" do not deserve hard covers. In the long run this form of presentation makes the material less accessible because of its restricted circulation. Moreover, the papers often seem to have been beaten forcibly into a shape that barely justifies their inclusion. If original observations happen to be included in the work of one of the authors, as likely as not it does not concern the theme of the symposium at all and would have found a better sounding-board in a widely circulated journal.

The present book is neither better nor worse than the average symposium. University libraries will be forced to buy it—like all the others—if they are to claim any completeness of their stacks. In the meantime, research workers in neuroanatomy will have to examine it for fear they are missing something important. These surely are poor reasons for publishing and buying any book.

MEDICAL NEWS *in brief*

(Continued from page 138)

ROLE OF SECONDARY OR PRECIPITATING CAUSES OF ASTHMATIC ATTACKS

Allergy, infection of the upper and lower respiratory tract and allergy with superimposed infection are now considered by most clinical observers to be primary causes of asthma. Therapy directed to these causes alone will not, in most instances, bring success. Success or failure in treatment, particularly of the non-allergic group of patients, where chronicity and intractability may be present, depends on the effective control of secondary or precipitating causes of attacks.

Secondary causes which have been chiefly stressed are climatic influences, physical agents—light, heat and cold; chemical and mechanical irritants; *acute infections of the respiratory system;* autonomic and hormonal imbalance and psychogenic factors.

In most instances the employment of antibiotics and adrenal corticosteroids, either alone or in combination, will tide an asthmatic patient over an acute paroxysm precipitated by respiratory infection. These therapeutic agents, in small maintenance doses, also have prophylactic value in lessening the tendency towards chronicity and intractability.

Other valuable adjuncts are breathing exercises to improve pulmonary ventilation and thereby lessen the tendency to emphysema, removal of chemical and mechanical irritants, correction of autonomic and hormonal imbalance, and lastly, a proper therapeutic approach to emotional problems.—S. H. Hurwitz, *Dis. Chest,* 32: 447, 1957.

TREATMENT OF RAGWEED HAY FEVER WITH INTRANASAL POWDERED HYDROCORTISONE

Corticosteroids have been very helpful in the symptomatic control of allergic disease, when administered either orally or parenterally for systemic effect, or topically for local effect. Lake and his colleagues from the Mayo Clinic (*Proc. Staff Meet. Mayo Clin.,* 32: 641, 1957) describe the results of the intranasal application of powdered hydrocortisone in 18 patients with ragweed hay fever.

The treatment was effective, and the recommended dose of 5 mg. three times daily was adequate for adults, but the dose of 5 mg. daily for children would be somewhat small for children of 7-8 years of age or older.

Local irritation occurred in only one patient and could not be indisputably ascribed to the preparation itself. No increase in incidence of secondary bacterial infection could be demonstrated, and in the doses recommended and used no evidence of hypercortisonism was noted.

It was concluded that intranasal insufflation of hydrocortisone is an effective, easily administered form of treatment in seasonal allergic rhinitis.

CYANACETHYDRAZIDE THERAPY IN PULMONARY TUBERCULOSIS

Cyanacetic acid hydrazide, which is structurally related to isoniazid, was given extensive clinical trial at a sanatorium by Kirshner (*Dis. Chest,* 32: 413, 1957). Clinical improvement and weight gain were common findings, but may be discounted because of the use of other drugs and excellent sanatorium care. However, because of absence of toxicity and frequency of sputum conversion (35%), it is evident that the drug has merit.

It has produced results in chronic cases under re-treatment as well

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MEDICAL NEWS *in brief*

(Continued from page 63)

as in new ones without evidence of toxicity. The problem of cross-resistance must be considered, since two patients who had had only a few weeks of isoniazid were found to be isoniazid-resistant after cyanacethydrazide therapy, and six long-term isoniazid patients who were isoniazid-susceptible showed isoniazid resistance after receiving cyanacethydrazide.

Hence cyanacethydrazide is an effective antituberculous agent, although less so than isoniazid. It is non-toxic and is well tolerated in large doses. Resistance studies indicate that it may possibly impair the usefulness of isoniazid. It appears to be of limited value in isoniazid-resistant patients. It is a valuable drug for those who cannot tolerate isoniazid.

EXPERIENCE WITH THE ANTICOAGULANT, MARCUMAR

The effects of the new anticoagulant drug Marcumar were studied by Ensor and Peters (*Ann. Int. Med.*, 47: 731, 1957) in 1729 patients over a period of two years. Conditions were classified under coronary disease, phlebitis, postoperative and postpartum. Each type of case presents its own difficulties and therapeutic problems.

A comparison of Marcumar with dicoumarol and Cumopyran in 288 long-term outpatient cases of coronary disease demonstrated the superiority of Marcumar, even when given in the most difficult cases. An additional spot-check of 161 outpatients with phlebitis and coronary disease verified this superiority. Marcumar by its prolonged duration of action gave a stable and satisfactory type of curve, and its advantages far overshadowed its initial delayed action. The use of vitamin K_1 therapy in correcting high prothrombin times is well recognized, but the writers stress the practical value of minimal oral doses, even as low as 1.25 mg., to correct threatening rises over the therapeutic level without over-correction.

In this entire series there was no death due to hæmorrhage, or case of bleeding in the 1080 coronary, phlebitis and postpartum cases. There were three cases of minimal hæmorrhage. One case of moderate gastro-intestinal hæmorrhage responded to blood transfusion and vitamin K_1 intravenously. Anticoagulants were then stopped. Ten days after discontinuance the patient died and autopsy revealed massive pulmonary embolism. Thus, even in postoperative prophylaxis in bowel, stomach and gall-bladder cases there was no instance of thrombo-embolism while the patient was under therapy.

The goal in anticoagulant therapy is not only adequate depression of blood prothrombin but also, and of equal importance, the constant maintenance of a stable level. This goal is more closely approached by Marcumar than by other anticoagulants.